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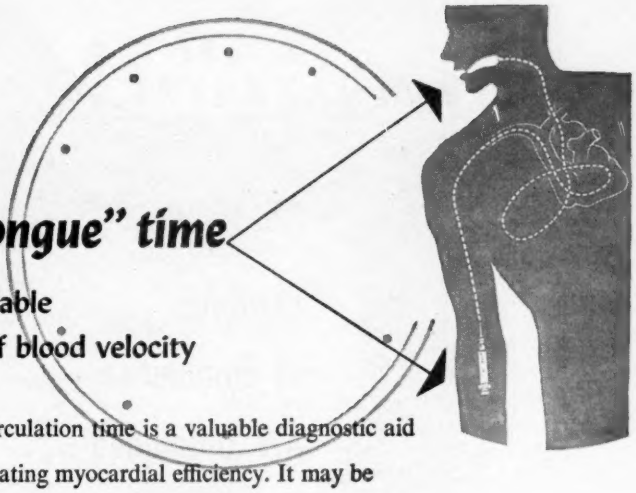

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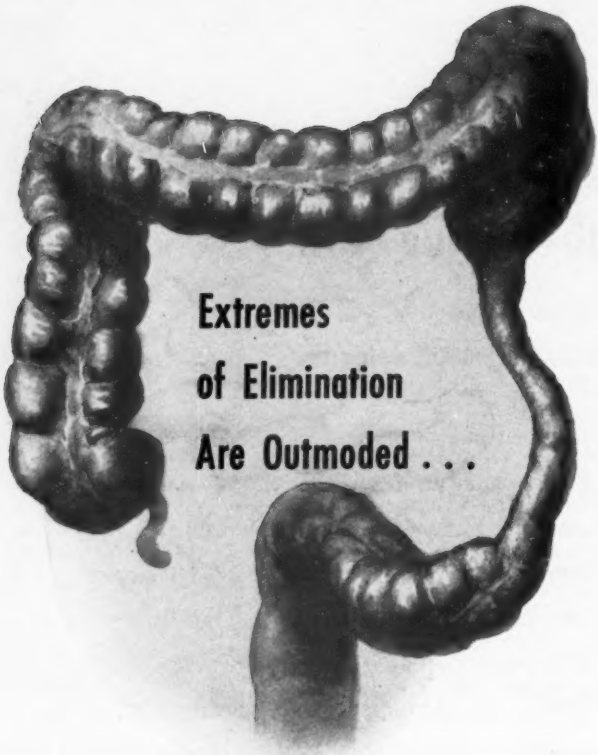

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RESEARCH IN THE SERVICE OF MEDICINE

A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 90 NOVEMBER 1952 NUMBER 5

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Editorials

SPURIOUS ANEMIA

AMONG the many pitfalls to which the physician is exposed, the interpretation of normalcy as it applies to clinical data continues in increased importance. Prolonged, usually expensive, and sometimes dangerous therapeutic programs are often pursued in response to the patient's demand for relief of an obscure symptom. These programs often originate in the mistaken interpretation of results of a given laboratory procedure as "too low" or "too high," the import reflecting a pathologic alteration of the related tissue or viscera. The article published by Wilson and Boyle in the present issue of the ARCHIVES forcibly calls attention again to this dilemma as it applies specifically to the evaluation of red blood cell counts.

It appears necessary to be reminded again of the fact that the red cell count gives only an estimate of the number of cells per unit volume of blood. Consequently, an increase or decrease in the red cell count does not of itself necessarily indicate an increase or decrease in the total mass of circulating red blood cells in the body as a whole nor, therefore, in the total oxygen-carrying capacity of the blood. Hemodilution and hemoconcentration, both acute and chronic, are variables, occurring both physiologically and in response to pathologic states, and may result in apparent anemia or polycythemia. When only apparent and not real, neither is responsible for the production of symptoms, and neither requires treatment upon a hematologic basis. Both, however, require proper identification. This can be accomplished only by including the data obtainable by determining the total body red cell volume.

Present procedures for computing the total circulating red cell mass comprise both indirect and direct methods. Indirect methods utilize the principle of dilution in the blood stream of small amounts of test substances to obtain the circulating plasma volume. From this, the red cell mass is calculated by obtaining from the hematocrit the ratio of red cells to plasma volume. Direct methods utilize the principle of dilution in the blood stream either of special red cells or of red cells that have been labeled by incorporating into the erythrocyte substances that can be identified. All procedures utilizing either of these approaches, unfortunately, are relatively complex and hence necessarily confined at present to the research laboratory.

The development of the indirect (plasma volume) methods utilizing dyes first devised by Keith, Rountree, and Geraghty [1] reached a point of limited accuracy

1. Keith, N. M.; Rountree, L. G., and Geraghty, J. T.: Method for Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547, 1915.

and convenience in the clinical method of Gibson and Evans [2] using the blue dye T-1824. However, the dye method has inherent defects that impair its usefulness. Rawson [3] has shown that the accuracy of the method depends upon rapid and complete binding of the dye to the albumin fraction of the plasma. After injection of T-1824, variable amounts of the dye are lost from the circulation because of the time interval for completion of the protein-binding action and the variable protein status of the subject. Additional loss of dye through phagocytosis of this substance by the reticuloendothelial cells of especially the liver and spleen further depletes the test material. The demonstration by Fine and Seligman [4] that iodine could be firmly bound to plasma protein and the recent work of Storaasli [5] and Crispell [6] and their associates, in which radioactive iodine I^{131} was bound to human serum albumin, resulted in a method applicable to routine clinical problems. This technique does not have some of the disadvantages and limitations of the dye methods. While the use of radioactive iodinated albumin seems an improvement over dye methods, it is of no more value than other methods in clinical states characterized by abnormal capillary permeability. It therefore appears likely that present indirect methods for the measurement of cell mass are intrinsically susceptible to considerable error in estimating the total body hematocrit.

Important progress in the determination of total circulating red cell mass was initiated by the work of Hahn and Hevesy,[7] who first demonstrated that the circulating red cell mass could be measured directly by tagging red blood cells with radioactive phosphorus, P^{32}. Subsequently, Hevesy and Zerahn [8] showed that P^{32} could be incorporated into red cells by incubation in vitro with radiophosphate and applied the method to the measurement of the body hematocrit in patients.[9] It has been proved that the radiophosphorus is metabolized by the red cell and not merely absorbed, a fact that adds materially to the accuracy of the method. Considerable data have been reported using this technique in comparison with other methods with some lack of uniformity in results by various investigators, probably because of differences in technique. A recent paper by Wasserman and co-workers,[10] comparing blood volumes simultaneously in 17 normal patients by the use of the dye T-1824 and P^{32}-labeled red cells, showed a poor correlation between these two methods for the circulating red cell mass, usually higher by the dye method. Other

2. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of Blood Volume: I. Clinical Application of Method Employing Azo Dye "Evans Blue" and Spectrophotometer, J. Clin. Invest. **16**:301, 1937.

3. Rawson, R. A.: Binding of T-1824 and Structurally Related Diazo Dyes by Plasma Proteins, Am. J. Physiol. **138**:708, 1943.

4. Fine, J., and Seligman, A. M.: Traumatic Shock: Study of Problem of "Lost Plasma" in Hemorrhagic Shock by Use of Radioactive Plasma Protein, J. Clin. Invest. **22**:285, 1943.

5. Storaasli, J. P.; Krieger, H.; Friedell, H. L., and Holden, W. D.: Use of Radioactive Iodinated Plasma Protein in Study of Blood Volume, Surg., Gynec. & Obst. **91**:458, 1950.

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8. Hevesy, G., and Zerahn, K.: Determination of Red Corpuscle Content, Acta physiol. scandinav. **4**:376, 1942.

9. Hevesy, G.: Radioactive Indicators, New York, Interscience Publishers, Inc., 1948.

10. Wasserman, L. R.; Yoh, T. F., and Rashkoff, I. A.: Blood Volume Determination: Comparisons of T-1824 and P^{32} Labeled Red Cell Methods, J. Lab. & Clin. Med. **37**:342, 1951.

methods determining directly the total circulating red blood cell mass, with the use of red cells labeled with radioactive iron ($Fe^{55, 59}$),[11] chromium (Cr^{51}),[12] and potassium (K^{42}),[13] currently under investigation seem less adaptable to the clinical laboratory. Historically, as research tools are refined and simplified they are made available to the routine clinical laboratories. It is to be hoped that continued investigation of direct methods to determine the red cell mass, especially the method using P^{32}-labeled cells,[14] results in a simplified procedure that is not beyond the resources of the modern clinical laboratory.

By the use of these cell volume techniques, it now appears that some of the unexplained anemias (and to a less extent the polycythemias) that have plagued both the practicing physician and the hematologist may, in fact, be spurious. The "physiologic" anemia of pregnancy was the first false anemia to be unmasked. It was found not to be an anemia at all, but simply the dilution of a normal total circulating red cell volume by increased total circulating plasma. Other recent publications have shown that some of the "anemias" found by blood counts in individual cases of leukemia,[15] portal cirrhosis,[16] and cancer[17] are characterized by normal circulating red cell masses. Wilson and Boyle's work seems to give a proper and, up to this time, the only rational explanation of the "anemia of neurasthenia." Reported differences in "normal" red cell counts found in different sections of the country, the reported low levels of hemoglobin in women as disclosed by blood donor records from the national headquarters of the American Red Cross,[18] as well as other instances in which lower than normal red cell counts or hemoglobin values are obtained, need restudy in view of these facts. The normality of the red blood cell level as determined by direct examination under the microscope and by the Wintrobe indices, together with other routine data, may not be adequate to evaluate a reported "low" or "high" blood cell count in terms of plasma dilution variations. As basic techniques become further simplified, it seems likely that the determination of the total red cell mass will be a necessary part of the routine blood count.

BRUCE K. WISEMAN, M.D.

11. Hahn, P. F.; Ross, J. F.; Bale, W. F., and Balfour, W. M.: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radio Iron and by Dye, J. Exper. Med. **75**:221, 1942. Gibson, J. G., II; Weiss, S.; Evans, R. D.; Peacock, W. C.; Irvine, J. W., Jr.; Good, W., and Kip, A. F.: Measurement of Circulating Red Cell Volume by Means of 2 Radioactive Isotopes of Iron, J. Clin. Invest. **25**:616, 1946.

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14. Reid, A. F., and Orr, M. K.: Rapid Method for Determining Blood Volumes by Use of P^{32} Labelled Red Cells, J. Clin. Invest. **29**:313, 1950.

15. Berlin, N. I.; Lawrence, J. H., and Gartland, J.: Blood Volume in Chronic Leukemia as Determined by P^{32} Labelled Red Blood Cells, J. Lab. & Clin. Med. **36**:435, 1950.

16. Hyde, G. M.; Berlin, N. I.; Parsons, R. J.; Lawrence, T. H., and Port, S.: Blood Volume in Portal Cirrhosis as Determined by P^{32} Labelled Red Blood Cells, J. Lab. & Clin. Med. **39**:347, 1952.

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18. Hervey, G. W.; McIntire, R. T., and Watson, V.: Low Hemoglobin Levels in Women as Revealed by Blood Donor Records, J. A. M. A. **149**:1127, 1952.

CORTICOTROPIN AND CORTISONE IN THE TREATMENT OF AGRANULOCYTOSIS AND THROMBOCYTOPENIC PURPURA

Report of Four Cases

MIKKO VIRKKUNEN, M.D.
HELSINKI, FINLAND

THE BENEFICIAL effect of corticotropin (ACTH) and cortisone in drug hypersensitivities is well known,[1] but only a few reports have been published on their usefulness in severe hypersensitive blood abnormalities. The efficacy of corticotropin and cortisone in agranulocytosis has been confirmed by Caldwell and co-workers [2] and by McMillin.[3] In the case reported by the former, treatment with cortisone was successful; the latter author described a rapid and complete remission with corticotropin therapy in a case of severe agranulocytosis. In both patients agranulocytosis resulted from sulfonamide therapy. Attempts to control thrombocytopenia with corticotropin or cortisone have given varying results. Combes and Costello [4] have reported a case in which severe thrombocytopenia with purpura and mucosal hemorrhage was arrested by treatment with cortisone. In patients with idiopathic thrombocytopenic purpura remissions induced by the administration of corticotropin or cortisone have also been reported [5]; on the other hand, there are cases in which no improvement has been noted after this therapy.[5c]

The following is a report on the effects of corticotropin and cortisone in two cases of agranulocytosis and two of thrombocytopenia. In the first two cases agranulocytosis developed in conjunction with treatment by a thiosemicarbazone

From the Medical Department of the Kivelä Hospital.

1. Carey, R. A.; Harvey, A. M.; Howard, J. E., and Wagley, P. F.: Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Drug Hypersensitivity Reactions, Bull. Johns Hopkins Hosp. **87**:354 (Nov.) 1950. Bordley, J. E.; Harvey, A. M.; Howard, J. E., and Newman, E. V.: Preliminary Report on the Use of ACTH in the Hypersensitive State, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, pp. 469.

2. Caldwell, A. L.; Adams, J. W.; Anderson, J. F. C., and Dick, A. A.: Agranulocytosis Treated with Cortisone, Canad. M. A. J. **62**:506 (May) 1950.

3. McMillin, J. S.: Successful Use of ACTH in the Treatment of Agranulocytosis Due to Sulfadiazine, Am. J. M. Sc. **222**:396 (Oct.) 1951.

4. Combes, F. C., and Costello, M. J.: Recent Advances in Dermatologic Therapy, New York J. Med. **50**:2678 (Nov. 15) 1950.

5. (*a*) Bethell, F. H.: Effect of ACTH and Cortisone on Plasmocytic Myeloma and Hypersplenic Syndromes, abstract of paper presented at the ACTH Adrenocortical Steroid Conference of the American Cancer Society, Oct. 28-29, 1950. (*b*) Revised Annotated Bibliography: Cortone (Cortisone, Compound E) and Related Hormonal Substances, 1951, Rahway, N. J., Merck & Co., Inc., p. 57. (*c*) Robson, H. N., and Duthie, J. J. R.: Capillary Resistance and Adrenocortical Activity, Brit. M. J. **2**:971 (Oct. 28) 1950.

(amithiozone ["conteben"]), while in the other two cases thrombocytopenia with purpura appeared after the administration of gold salts.

REPORT OF CASES

CASE 1.—A woman aged 50 years in the spring of 1950 had rather quick development of rheumatoid arthritis after an irregular occurrence of intermittent hydrops in both knees over a period of several years. By the end of September, 1950, several joints were involved, and the erythrocyte sedimentation rate (Westergren) was 61 mm. in an hour. Thiosemicarbazone therapy [6] was instituted in a dosage of 50 mg. three times daily. Considerable remission took place in a fortnight, with the sedimentation rate falling to 12 mm. The leucocyte count, determined once a week, ranged between 7,200 and 6,000. On Oct. 31, 1950, after the administration of a total of 7 gm. of thiosemicarbazone over five weeks, the patient contracted fever, chills, nausea, and pain in the extremities. Administration of the drug was discontinued, and the following day the patient was admitted to the hospital. Her condition seemed to be satisfactory. The leucocyte count was 2,600, and there was no fever. On the days following, however, a rapid impairment took place. The patient had a high fever, and the leucocyte count fell to the minimum of 800 per cubic millimeter, with 4% neutrophiles, 7% monocytes, and 89% lymphocytes (Chart 1). The sternal marrow was hypoplastic with marked maturation arrest of the myeloid cells, among which only promyelocytes and myeloblasts were found. No remission was noted in the blood cell count after the administration of penicillin and repeated blood transfusions for six days. On the fourth day, pneumonia appeared in the right lung. In addition, tonsillitis and proctitis developed without necrotization of the mucous membranes, and pericardial friction appeared. On the sixth day, some corticotropin was received and could be administered to the patient; at that time, she was already comatose and extremely ill. The response to corticotropin was dramatic. Within 18 hours, after three injections of 20 mg. of corticotropin, the temperature returned to normal and the white blood cell count rose from 1,240 to 2,500 per cubic millimeter. A total of 250 mg. of corticotropin was administered over a period of four days, during which a transient leucocytosis developed, common during the remission phase of agranulocytosis. After that, the leucocyte count returned to normal and remained normal up to the present (April 15, 1952) without any further medication.

CASE 2.—A woman aged 48 years had had rheumatoid arthritis for more than a year and had been treated with gold salts for seven months. Since there was no response to treatment, the patient was admitted to the hospital on Jan. 26, 1951, on account of her impaired condition. For five weeks she received a total of 6.5 gm. of thiosemicarbazone. The articular symptoms subsided slowly, and the sedimentation rate (Westergren) fell from 49 to 19 mm. in an hour. Weekly leucocyte counts ranged from 6,200 to 5,000; by March 8, 1951, however, the count had fallen to 1,800 (Chart 2), and the administration of the drug was discontinued. Two days later the patient had a slight rise in temperature, and penicillin therapy was instituted. After two further days the temperature suddenly rose, and tonsillitis appeared. Corticotropin therapy was instituted; the dose was 40 mg. on the first day and 80 mg. on the second. During these two days the leucocyte count rose from 1,900 to 4,000 and the neutrophiles increased from 2.5 to 51%.

6. Stimulated by observations of Heilmeyer (Neuartige Wirkungen der Thiosemicarbazone bei hyperergischen Prozessen, Klin. Wchnschr. **26**:649 [Nov. 1] 1948; Die Beeinflussung der Entzündungsbereitschaft und der Plasmakolloide durch das Thiosemicarbazonderivat TB 1 im Vergleich zu den Wirkungen der Hormone der Nebennierenrinde und der Hypophyse und ihre Bedeutung für das Rheumaproblem, ibid. **28**:254 [April 15] 1950) of Germany, I carried out experiments on the use of thiosemicarbazone in the treatment of rheumatoid arthritis. Heilmeyer noted that in pulmonary tuberculosis thiosemicarbazone therapy was followed by a rapid return of the sedimentation rate to normal without improvement in the other clinical symptoms of tuberculosis. In rheumatoid arthritis, however, he found not only that the sedimentation rate returned to normal but that there was often also a rapid and distinct disappearance of joint symptoms after the administration of thiosemicarbazone. From this he inferred that the drug probably had some therapeutic value in rheumatoid arthritis.

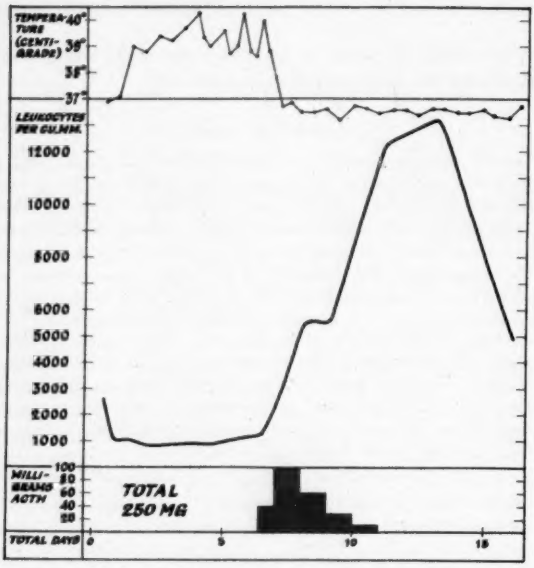

Chart 1 (Case 1).—Effect of corticotropin (ACTH) administration on leucocyte count and body temperature in agranulocytosis.

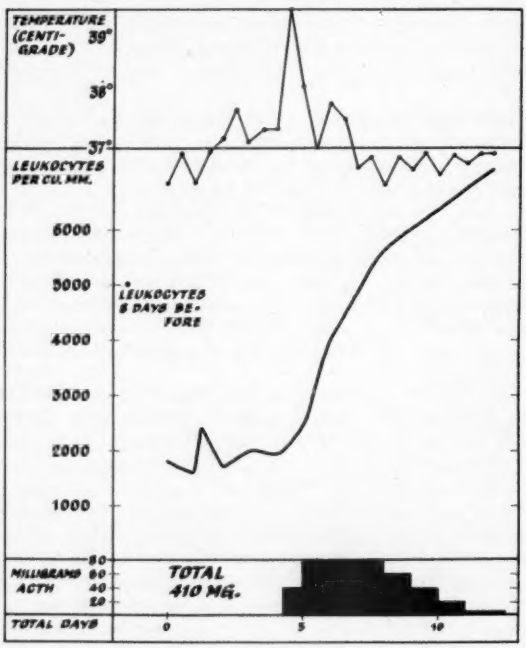

Chart 2 (Case 2).—Effect of corticotropin (ACTH) administration on leucocyte count and body temperature in agranulocytosis.

After this, the blood cell count remained normal up to the present (April 15, 1952) without any further therapy. Prior to the administration of corticotropin, a sternal puncture disclosed mild myeloid hypoplasia, a lack of metamyelocytes and mature granulocytes, and toxic changes in numerous myeloid cells.

CASE 3.—A woman aged 50 years had had symptoms of rheumatoid arthritis for more than 10 years. The disease remained benign for a long time, with remissions spontaneously and during pregnancies. On account of her impaired condition, the patient was admitted to the hospital on March 20, 1951. Gold therapy was instituted, but it had to be discontinued after six weeks (May 12, 1951) because the blood cell count revealed an eosinophilia (20%). Until that time the patient had received a total of 0.2 gm. of gold sodium thiomalate (myochrysine®), and the thrombocyte (platelet) count had ranged between 185,000 and 149,000 per cubic millimeter. After this treatment, the patient's condition was good and there was a distinct improvement in the symptoms of arthritis. She was discharged on May 15, 1951; at home, she took no drugs except 0.5 gm. of acetylsalicylic acid daily. Four months later thrombocytopenia developed suddenly,

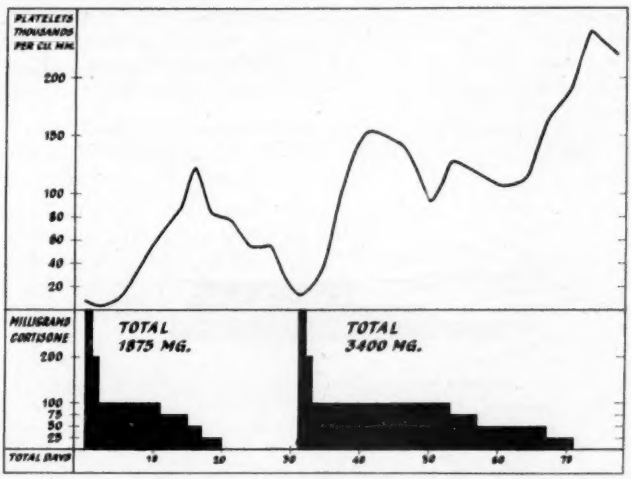

Chart 3 (Case 3).—Effect of cortisone administration on thrombocyte (platelet) count in thrombocytopenia.

with extensive bruises and mucosal hemorrhages. At the same time there was a transient itching rash around the eyes and below the breasts. The patient was readmitted to the hospital on Sept. 17, 1951, with a thrombocyte count of 8,000 per cubic millimeter (Chart 3), a bleeding time of 12 minutes 45 seconds, and a clotting time of 8 minutes 15 seconds. No anemia was present. Cortisone therapy was started, the patient receiving 300 mg. on the first day, 200 mg. on the second day, and after that 100 mg. daily. No further cutaneous hemorrhages were noted, and in two days the bleeding time fell to 5 minutes and the coagulation time to 2 minutes 30 seconds. The thrombocyte count rose steadily and was 123,000 per cubic millimeter on the 15th day, after the administration of a total of 1.7 gm. of cortisone. Cessation of cortisone therapy, however, resulted in a new fall in the thrombocyte count. Eleven days after the cessation of treatment, the thrombocyte count was 13,000 per cubic millimeter, and purpuric spots made their reappearance. A new course of cortisone therapy was instituted, with the administration of a total of 3.4 gm. of cortisone over a period of 40 days. During this time the thrombocyte count rose slowly to 220,000 per cubic millimeter. There has been no relapse within five months of the end of the treatment.

CASE 4.—A woman aged 40 years was admitted to the hospital on March 8, 1951, because of thrombocytopenia with cutaneous and mucosal hemorrhages.

Six years previously she had had rheumatoid arthritis, and, since the symptoms became severe, gold therapy was instituted in June, 1950. After the administration of a total of 0.3 gm. of gold sodium thiomalate for two months, a generalized dermatitis appeared. The administration of gold was discontinued, and the patient received a total of 3.75 gm. of dimercaprol (BAL) for 11 days, after which dermatitis subsided. Repeated blood cell counts during gold and dimercaprol therapy showed normal thrombocyte and differential leucocyte counts, except for a transient eosinophilia during the dermatitic phase. In January, 1951, four months after the cessation of gold treatment, the patient found that bruises readily appeared on her skin; there was occasional epistaxis, and the menses were attended with profuse bleedings. The signs of hemorrhagic diathesis had been present for more than two months by the time the patient was admitted to the hospital (March 8, 1951). For the past six months she had not taken any drugs except acetylsalicylic acid in occasional doses of 0.5 gm. and a total of 9 gm. of sulfadiazine in four days in February, 1951, which produced a temporary skin rash.

Examination of the blood on admission showed a moderate anemia (hemoglobin concentration, 8.35 gm. per 100 cc.), a normal leucocyte count, a long bleeding time (21 minutes 30 seconds), and a normal coagulation time (3 minutes 30 seconds). The lack of thrombocytes was almost complete; in a smear preparation only 1 or 2 thrombocytes were found per 1,000 erythrocytes. Corticotropin therapy was started, with no other treatment. In the first two weeks a total of

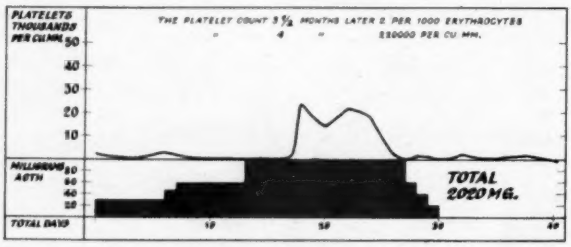

Chart 4 (Case 4).—Effect of corticotropin (ACTH) administration on thrombocyte (platelet) count in thrombocytopenia.

585 mg. of corticotropin was given in daily doses of 30 to 60 mg. The lack of thrombocytes continued, however, during the medication, and fresh bruises appeared. For the subsequent 14 days daily doses of 100 mg. were administered and the thrombocytes rose transiently to 24,000 per cubic millimeter, but only a week later they were again completely lacking (1 to 2 thrombocytes per 1,000 erythrocytes). The bleeding time, however, returned to normal during the second period of treatment, and there were no fresh cutaneous or mucosal hemorrhages, except for a few purpuric spots which appeared occasionally on the legs. The menstrual flow, too, returned to normal. The patient's condition was good, and at the beginning of May, 1951, she resumed her work as an office clerk. Numerous follow-up studies showed that to the end of July, 1951, thrombocytes were lacking as before. At the next follow-up, in mid-August, four months after the end of corticotropin treatment, the thrombocyte count, surprisingly, was 220,000 per cubic millimeter and has remained normal for eight months.

COMMENT

In both cases of agranulocytosis the therapeutic effect of corticotropin was dramatic. In Case 1 the condition of the patient was critical, and I believe that recovery would not have been possible without corticotropin. In the second case the agranulocytosis was comparatively mild, but it, too, showed no signs of remission before hormonal therapy was started. These cases thus confirm earlier reports of

the usefulness of corticotropin in therapy of agranulocytosis and suggest that the possibilities of controlling this dangerous blood dyscrasia have essentially increased.

The two cases of thrombocytopenia were atypical in that the condition developed four months after the discontinuance of gold therapy. Such a late occurrence of thrombocytopenia, however, is known to occur in connection with gold therapy.[7] Both patients had other manifestations of drug hypersensitivity, i. e., marked eosinophilia and dermatitis. The presence of idiopathic thrombocytopenia was thus improbable, and the condition was taken to be a late complication of gold therapy. In Case 3, in which the disease had been present for a short time and the disappearance of thrombocytes was not complete, a week's treatment with cortisone in ordinary doses was followed by a rise of the thrombocyte count to the normal level. The quick recurrence of thrombocytopenia with cutaneous hemorrhages which followed the discontinuance of the therapy shows that the remission was not spontaneous but is to be ascribed to the administration of cortisone. A new course of therapy, which lasted for more than a month, was needed to return the thrombocyte count to normal.

In the second case thrombocytopenia purpura was severe, with hemorrhagic symptoms for more than two months prior to corticotropin therapy. In spite of treatment for a whole month, during which 2 gm. of corticotropin was given, the thrombocyte count showed no change, apart from a negligible rise noted for a few days at the beginning of the treatment. There was a remission, but a spontaneous one, and it did not take place until four months after the cessation of treatment. On the other hand, a considerable change took place in the patient's condition during corticotropin therapy, although the lack of thrombocytes continued. The bleeding tendency disappeared and did not recur. There were no fresh cutaneous or mucosal hemorrhages, and the menstrual flow, which had been profuse on three occasions prior to the administration of corticotropin, was normal after the therapy was started. This case showed clearly what has been known before, that in thrombocytopenic purpura the tendency to hemorrhage does not always parallel the decrease in the number of thrombocytes. Corticotropin proved to have an unquestionable effect on the hemorrhagic phenomena, but it had no effect on thrombocytopenia itself. This speaks for the view that the antihemorrhagic effect of corticotropin is due to increased capillary resistance, as noted by Robson and Duthie [8c] during corticotropin therapy of thrombocytopenic purpura.

Permanent recovery was achieved in both cases of agranulocytosis after short-term administration of corticotropin and the withdrawal of the offending drug. In the cases of thrombocytopenia due to gold salts, however, more extensive hormonal treatment seemed to be necessary for permanent remission. The delayed recovery in the latter cases may be explained on the basis of the very slow excretion of gold, which makes it impossible to inhibit the continuing noxious effects of this drug.

SUMMARY

Two cases of agranulocytosis due to the administration of thiosemicarbazone, in one of which the condition was particularly severe, are reported. In both cases

7. Sundelin, F.: Die Goldbehandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen, Acta med. scandinav., Supp. 117, p. 217, 1941.

corticotropin (ACTH) therapy was followed by permanent recovery within two days.

In a case of moderately severe thrombocytopenic purpura after gold therapy a fortnight's treatment with cortisone resulted in a remission of the thrombocyte count, but the thrombocytopenia recurred immediately after the end of treatment. A permanent return of the thrombocyte count to normal ensued during a new course of cortisone treatment given for more than a month.

In a case of severe thrombocytopenia which appeared after gold therapy, a total of 2 gm. of corticotropin was administered over a month, without any improvement in the complete lack of thrombocytes. In the course of treatment, however, hemorrhagic phenomena disappeared to remain permanently absent, but complete thrombocytopenia persisted until four months after treatment, when the thrombocyte count, in all probability spontaneously returned to normal.

TREATMENT OF HYPERTENSION WITH ORALLY AND PARENTERALLY ADMINISTERED PURIFIED EXTRACTS OF VERATRUM VIRIDE

Comparison with Ganglionic (Hexamethonium) and Adrenergic Blocking Agents

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THE TREATMENT of hypertension in the past has been generally unsatisfactory, despite the introduction of many and varied forms of therapy. In the last few years, however, the purification of the Veratrum alkaloids and the synthesis of several new compounds which produce ganglionic or adrenergic blockade has led to a more specific approach to the treatment of hypertension. Increasing effort is being exerted to find an effective agent which will lower blood pressure and thus arrest the progression of the disease. Frequently, reports by original investigators are very enthusiastic, yet when the drugs are distributed for general use the results cannot be duplicated. This has been particularly true when the preliminary drug evaluation was carried out on hospitalized patients who were under strict control of highly specialized investigative teams. Failure of physicians in general office practice to reduplicate the results is largely due to the fact that exact control of the patient's activities and drug administration cannot be regulated as well on an outpatient basis. It is the purpose of this paper to report our experience with the oral use of two semipurified extracts of Veratrum viride ("anatensol" and alkavervir [veriloid®] [1]) during the last two and one-half years, and to compare their therapeutic efficacy with that reported by other workers using veratrum preparations and with our results using some of the newer ganglionic and adrenergic blocking agents in similar circumstances. Since the majority of these studies were conducted on an outclinic basis, the problems encountered will closely parallel those which are met in general office practice. An analysis of the observations should serve as a gauge of the therapeutic results the practitioner may anticipate with these agents. In addition, the effectiveness of continuous intravenous infusion of alkavervir in the treatment of hypertensive emergencies is reported.

METHODS AND MATERIAL

Sixty-one patients who received Veratrum viride preparations orally were studied (Tables 1 and 2). All patients had an average supine and upright blood pressure greater than 160/100 during the control periods. The control blood pressure for each patient consisted of the average of repeated blood-pressure determinations taken in the supine and upright positions over a

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1. "Anatensol" (now known as "vergitryl") was supplied through the courtesy of E. R. Squibb & Sons, New York 22. Veriloid® was supplied through the courtesy of Riker Laboratories, Inc., Los Angeles 48.

minimum of three to four weeks. Some of the patients had been followed up to two years, receiving only symptomatic therapy. The post-treatment blood pressure is the average of all values obtained following the titration period (during which time the blood pressure and drug dosage were being stabilized). During the control period, all patients had the usual clinical and laboratory studies performed to establish the etiological diagnosis, the presence or absence of complications, and the probable prognosis of their hypertensive disease. These studies included a history and physical examination, complete blood count, urinalysis, Fishberg concentration test, phenolsulfonphthalein test, blood urea nitrogen determination, intravenous pyelogram, electrocardiogram, and chest roentgenogram. In those patients in whom there was any suggestion of a pheochromocytoma, a piperoxan (benzodioxane) test was done. These tests were repeated during therapy when indicated. A few patients had renal clearance studies done according to the methods of Goldring and Chasis.[2] Seven patients were found to have hypertension associated with chronic glomerulonephritis, while in the remaining 54 the causation was unknown (essential hypertension).

Thirty-one patients were given "anatensol" by mouth, and 30 received alkavervir orally. Eight of the patients receiving "anatensol" and 10 receiving alkavervir were private patients. The remainder were seen in the cardiac clinic of the hospital. The therapeutic dose was determined by titration in all patients. In those receiving "anatensol" treatment was started with 0.4 to 0.8 mg.[3] before or after each meal and at bedtime, with a gradual increase in the dose each week either until a satisfactory hypotensive response had been obtained or until incapacitating side-reactions ensued, preventing a further increase in the dose. If blood-pressure reduction was not obtained before side-reactions ensued, attempts were made to space the drug administration more evenly and more frequently. This was an effort to circumvent peaking of drug concentration in the blood and thus circumvent the toxic reactions. Patients receiving alkavervir orally were treated in a similar manner, using 1 mg. after each meal and at bedtime as the initial dose. The dose was then progressively increased. After therapy was started, all patients were seen at weekly intervals as long as the blood pressure remained lowered or until side-reactions from the drug necessitated interruption of therapy. It is to be noted, however, that initally some of the private patients were seen more frequently and were more intelligent, factors which permitted more rapid titration. The patients who were treated with orally administered ganglionic and adrenergic blocking agents were placed on a similar therapeutic titration regimen. The type of patients and the severity of the disease were approximately similar in all groups studied.

Thirty-nine additional patients received alkavervir intravenously and were hospitalized during therapy. Eight patients in this group had hypertension associated with chronic glomerulonephritis. The remainder were considered to have essential hypertension. Many of these patients had hypertensive encephalopathy or were admitted because of a hypertensive crisis. Usually a priming dose of 0.5 γ of alkavervir per kilogram of body weight per minute was given intravenously until a satisfactory hypotensive response was obtained. This was followed by an infusion containing 3.6 mg. of alkavervir per liter, at a rate of 10 to 100 drops per minute, depending on the blood-pressure response. This infusion was continued for 18 to 96 hours in 17 patients and for 4 to 8 hours in the other 22 patients. After the intravenous infusion of alkavervir, administration of some form of oral therapy or of alkavervir intramuscularly was started.[4] Cerebral blood flow studies were done on some of these patients in order to evaluate the cerebrohemodynamic effects of acute reduction in blood pressure with intravenous infusions of alkavervir.

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2. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, Commonwealth Fund, Division of Publications, 1944.

3. A recent communication indicates that these tablets have approximately twice the therapeutic activity of the present "vergitryl" tablets when compared milligram for milligram because of the use of a new standard. It was also indicated that in some patients the difference between the dose necessary to obtain a hypotensive response and that causing toxic symptoms was as little as one-quarter to one-half tablet (E. R. Squibb & Sons: Personal communication to the authors).

4. Johnson, I., and Mills, L. C.: Intramuscular Veriloid in the Treatment of Hypertension, Federation Proc. **11**:360 (March) 1952.

TABLE 1.—*Blood-Pressure and Clinical Response to "Anatensol" Given Orally**

Case No.	Age	Sex	Duration of Hypertension, Yr.†	Dose, Mg./Day	Blood Pressure			Duration of Treatment, Wk.	Diagnosis	Clinical Status at Present
					Control	After Drug‡	Difference			
			Group 1A: Reduction in Blood Pressure of More Than 40 Mm. Systolic and 20 Mm. Diastolic (MBP >26 Mm.)							
1	38	M	1	5.6	300/160	230/130	70/30	35	MHCVD, ANS	Died of uremia
2	62	M	Unknown	10.4	210/140	170/110	40/30	13	EH, ANS	Discontinued therapy because of nausea and vomiting
Mean	50			8.0	255/150	200/120	55/30	24		
			Group 1B: Reduction in Blood Pressure of More Than 20 Mm. Systolic and 10 Mm. Diastolic (MBP >13 Mm. But <40 Mm. Syst. and 20 Mm. Diast.)							
3	26	M	0.3	7.2	170/110	140/80	30/30	104	EH	No toxic effects; improved§
4	28	M	Unknown	5.2	180/125	145/115	35/10	52	CGN	Improved§
5	58	M	3	6.0	220/130	200/120	20/10	20	EH	No toxic effects; unimproved§
6	46	F	6	4.4	190/114	170/104	20/10	26	EH	Intermittent nausea and vomiting; discontinuance of therapy
7	42	F	2	12.0	220/138	185/110	32/28	8	EH	Nausea and vomiting; patient refused therapy
8	41	F	1.2	4.4	198/121	173/98	25/23	7	HCVD	Nausea and anorexia; unimproved; discontinuance of therapy
Mean	40		2.5	6.2	196/123	169/104	27/19	37		
Grand Mean	43		2.3	6.7	211/130	177/108	34/22	34		
			Group 1C: Unresponsive Patients (23 Patients)							
Mean values	48		7.9	7.3	202/125	197/121	5/4	11	EH (6 pt.) HCVD (16 pt.) CGN (1 pt.)	All had toxic reactions before hypotensive response obtained; 1 patient died of uremia (ANS)

* Abbreviations used are MBP, mean blood pressure (one-third pulse pressure plus diastolic pressure); MHCVD, malignant hypertensive cardiovascular disease; ANS, arteriolar nephrosclerosis; EH, essential hypertension; CGN, chronic glomerulonephritis; HCVD, hypertensive cardiovascular disease, and pt., patient.

† Duration from history only in most patients.

‡ Average of observations after maximum tolerated dose of drug established.

§ Continues to take drug.

TABLE 2.—*Blood-Pressure and Clinical Response to Alkavervir Given Orally**

Case No.	Age	Sex	Duration of Hypertension, Yr.†	Dose, Mg./Day	Blood Pressure			Pulse Rate		Duration of Treatment, Wk.	Diagnosis	Toxic Effects and Comment
					Control	After Drug‡	Difference	Control	After Drug‡			
Group 2A: Reduction in Blood Pressure of More Than 40 Mm. Systolic and 20 Mm. Diastolic (MBP >26 Mm.)												
1	37	M	0.5	38	250/148	196/114	54/34	74	68	104	MHCVD	Occasional nausea and vomiting§
2	52	F	2.5	17	263/160	190/127	73/33	84	72	54	EH	Occasional nausea and vomiting§
3	49	M	2.0	8	170/110	130/80	40/30	69	59	52	EH	NTE; improved§
4	46	M	2.1	21	246/148	182/108	64/40	78	74	48	EH	Discontinued therapy‖
5	36	M	0.5	24	290/160	210/140	80/20	70	68	35	MHCVD	NTE; death of uremia
6	32	M	3.0	8	300/200	190/130	110/70	90	78	26	MHCVD	Improved for 6 mo.¶
7	68	M	8.0	16	248/138	180/104	68/34	84	68	13	EH	Nausea and vomiting; discontinued therapy
Mean	46		2.7	19	252/152	183/115	69/37	80	70	47		
Group 2B: Reduction in Blood Pressure of More Than 20 Mm. Systolic and 10 Mm. Diastolic (MBP >13 Mm. But <40 Mm. Syst. and 20 Mm. Diast.)												
8	48	F	0.7	20	206/116	168/98	38/18	70	64	112	EH	Improved; nausea and vomiting§
9	28	M	3.5	10	198/124	167/100	31/24	80	66	56	EH	Occasional nausea and vomiting§
10	18	M	1.5	18	170/110	148/90	22/20	76	60	52	EH	Improved with therapy#
11	38	M	1.5	13	248/148	220/130	28/18	76	73	52	MHCVD	NTE; died
12	39	F	7.2	22	256/146	218/128	38/18	74	60	47	EH	Nausea and vomiting; discontinued therapy‖
13	38	M	0.5	14	220/140	190/110	30/30	72	58	26	EH	NTE**
14	24	F	0.3	12	210/120	176/100	34/20	86	76	17	EH	Occasional nausea and vomiting**
15	52	F	15.0	10	190/138	160/110	30/28	70	56	17	MHCVD	NTE; died
Mean	36		3.8	15	212/130	181/100	31/21	76	64	47		
Grand mean	41		3.3	17	231/140	181/111	50/29	78	67	47		
Group 2C: Unresponsive Patients (15 Patients)												
Mean values	50	4	4.8	19	212/126	209/118	3/8	84	78	49	EH (10 pt.) CGN (5 pt.) Death, uremia (1 pt.) Death, CVA (1 pt.)	All had toxic reactions before hypotensive response obtained

* Abbreviations used are NTE, no toxic effects; CVA, cerebrovascular accident. For explanation of other abbreviations see footnote to Table 1.
† Duration from history only in most patients.
‡ Average of observations after maximum tolerated dose of drug established.
§ Continues to take drug.
‖ Repeated vascular collapse reactions.
¶ Infection after tooth extraction with loss of response; toxic effects with increased dose; discontinuance of therapy.
# Nausea and vomiting at end of one year of therapy with return of blood pressure to control levels.
** Failed to return.

RESULTS

Table 1 shows the results of administration of "anatensol" by mouth to 31 patients. The status of these patients at present is given in the last column of Table 1.

There were eight patients (26%) in whom the blood pressure fell 20 mm. or more of mercury systolic and 10 mm. or more of mercury diastolic below the control values. In only two of these patients was the fall greater than 40/20. In the remaining 23 patients there was no response. The average age and average control pressures were similar in those responding and in those with no hypotensive effect. The average daily dose for the former was 6.7 mg. per day, as compared with 7.3 mg. per day for the latter, this indicating that the unresponsive group actually received slightly larger doses of the drug. The percentage of men responding was

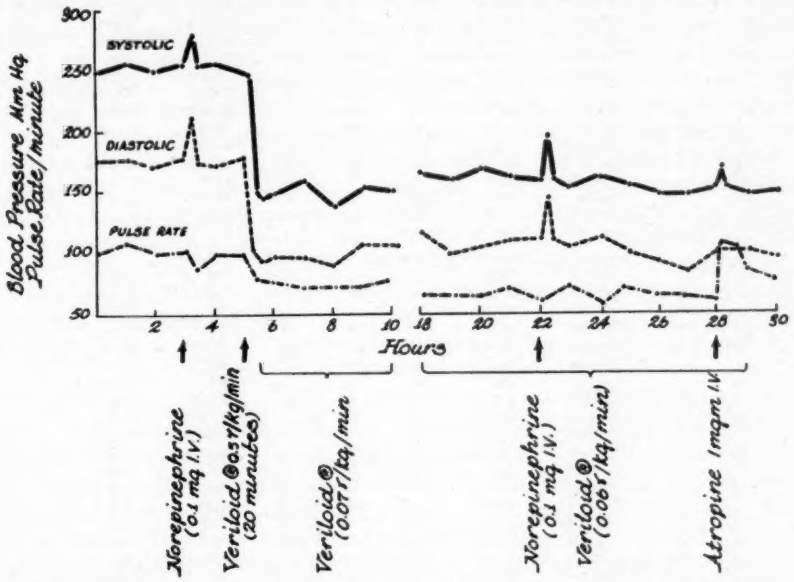

Fig. 1.—A typical response to alkavervir (veriloid®) given intravenously. There was a marked reduction in systolic and diastolic blood pressure and in pulse rate. This reduction was maintained at an almost constant level by continuous infusion of alkavervir. There was no difference in response to arterenol (nor-epinephrine) during infusion of alkavervir as compared with the control response. Administration of atropine blocked the bradycardia produced by the drug, but did not alter the hypotensive effect.

greater than the percentage for the group as a whole. The patients responding had had known hypertension for an average of 2.3 years, as compared with 7.9 years for the remainder. Even in those patients who had a hypotensive response it was difficult to continue the therapy for prolonged periods because the necessary dose continually bordered at the toxic level. Of the eight patients in whom the blood pressure decreased more than 20/10, effective medication could be administered for more than one year to only two. However, one other patient in the responding group also continues to take the drug but has been followed for only 26 weeks. In only 1 (Case 3, Table 1) of the 31 patients was it possible to reduce the blood pressure to normotensive values and retain it there.

Table 2 shows the results obtained with the oral use of alkavervir in 30 patients. In 15 of the 30 patients (50%) there was a drop in blood pressure greater than 20 systolic and 10 diastolic (average 50/29). Seven of the 15 responded with a fall

TABLE 3.—*Blood-Pressure and Symptomatic Response to Alkavervir Given Intravenously**

Case No.	Age	Duration of Hypertension, Yr.†	Blood Pressure: Control	Blood Pressure: After Drug‡	Pulse Rate: Control	Pulse Rate: After Drug‡	Duration of Infusion, Hr.	Diagnosis	Side-Reactions	Symptomatic Improvement
			Group 3A:	Patients Receiving	Prolonged	Alkavervir	Infusion			
1	56	1	240/162	150/100	76	72	96	HCVD	None	0
2	55	0.5	225/145	180/120	100	50	96	CGN	None	1+
3	36	7	300/210	180/125	82	80	96	HCVD	Weakness	3+
4	42	10	210/140	156/104	77	50	72	CGN	None	2+
5	27	4	265/170	155/105	104	70	72	HCVD	N & V	3+
6	60	7	235/150	170/110	84	70	72	HCVD	Nausea	3+
7	53	2	190/125	130/110	80	86	72	HCVD	H & N	2+
8	24	8	200/150	155/90	66	44	48	HCVD	None	2+
9	28	13	224/162	160/110	107	108	48	CGN	Restlessness	3+
10	48	1	230/164	150/90	120	100	48	HCVD	Dizziness; W & N	3+
11	48	0.3	310/220	240/160	72	58	48	HCVD	H & W	0
12	52	10	248/130	162/90	80	64	48	HCVD	Dizziness	3+
13	49	1	200/140	130/100	84	76	24	HCVD	N & V§	0
14	51	2	290/160	140/120	100	60	24	HCVD	H & V§	1+
15	33	6	190/120	110/66	90	70	24	CGN	N & V§	2+
16	54	1	300/210	158/110	90	56	24	HCVD	H & W§	3+
17	29	6	220/160	130/95	80	64	18	CGN	None	Died
Mean	44	4.7	243/160	156/107‖	88	69‖	55			
			Group 3B:	Patients Receiving	Short-Term	Alkavervir	Infusion			
18	41	1	180/104	133/81	107	108	4	EH	None	2+
19	41	4	206/133	150/110	128	102	6	EH	N & V	2+
20	49	4	240/160	156/114	81	62	2	EH	Nausea	2+
21	45	10	250/140	130/90	80	60	3	EH	None	1+
22	28	0.5	250/180	120/110	129	108	8	HCVD	None	3+
23	44	2	236/140	150/106	104	88	8	HCVD	None	3+
24	33	1	250/175	108/78	132	84	6	EH	None	2+
25	52	10	204/130	140/100	92	72	4	HCVD	H, N, & V	1+
26	48	4	250/150	150/100	94	80	8	HCVD	N & V	3+
27	34	1	210/135	100/70	80	64	6	HCVD	None	0
28	32	0.5	196/116	144/94	72	64	4	HCVD	None	2+
29	41	2.0	184/112	104/62	92	56	4	HCVD	None	1+
30	44	4.0	240/156	148/84	68	56	6	CGN	N & salivation	3+
31	28	6.0	186/118	160/96	72	56	8	CGN	N & V	1+
32	34	0.3	210/118	160/90	92	76	8	HCVD	None	2+
33	54	1.0	254/134	156/84	80	68	8	HCVD	Weakness	3+
34	42	0.5	196/124	158/90	88	80	8	HCVD	Nausea	3+
35	34	1.3	232/156	176/104	88	72	8	HCVD	Nausea	2+
36	29	6.5	240/140	160/100	76	64	6	HCVD	N & salivation	1+
37	58	2.5	218/112	156/88	88	56	6	CGN	None	1+
38	42	4	234/140	172/116	84	76	6	HCVD	None	0
39	30	1	220/138	180/104	92	84	6	HCVD	None	2+
Mean	41	3.5	222/126	146/94‖	92	74‖	6.0			
Grand mean	42	3.7	231/147	150/100‖	90	72‖	27			

* Abbreviations used are H, hiccoughs; W, weakness; N, nausea, and V, vomiting. See footnotes to Tables 1 and 2 for explanation of other abbreviations. In column headed "Symptomatic Improvement," 0 indicates none; 1+, slight; 2+, moderate, and 3+, complete disappearance of hypertensive symptoms. This applies only to improvement noted during and immediately after alkavervir infusion.

† Duration from history only in most patients.

‡ Average of observations after hypotensive response established and stabilized.

§ Infusion stopped at this time because of severe toxic symptoms.

‖ Statistically significant change from control value ($P = <0.01$).

greater than 40/20 (average 69/37). In comparison of the patients responding with those not responding, it was again noted that they were of similar ages, that the percentage of men responding was greater than the percentage for the group as a

whole, that the known duration of the hypertension was less, and that the average daily dose in patients showing response was less than that in those not responding (17 : 19 mg.). It is again noteworthy that, although a significant reduction in blood pressure was noted in about one-fourth of the patients, in only 1 of the 30, or 3%, did the blood pressure return to normotensive levels (Case 3, Table 2). The toxic manifestations limiting adequate dosage to obtain normotensive blood pressure were essentially the same as with "anatensol." Of the 15 patients originally responding, 5 have been able to continue therapy for one to two years.

The effects of the intravenous administration of alkavervir in 39 patients are shown in Table 3 and in 1 typical patient in Figure 1. These 39 patients were comparable with those in other groups with respect to age and duration of known hypertension, but had a slightly higher average control blood pressure. In addition, many had encephalopathic manifestations or were experiencing acute exacerbations of their hypertension (hypertensive crises). Twenty-two patients received alkavervir by continuous infusion over a 4- to 8-hour period, and 17 received it over an 18- to 96-hour period (average, 55 hours). In 35 of the patients (90%) the fall in blood pressure was greater than 40/20, and in the other 4 it was greater than 20/10. The average decrease for the group was 81/47. In addition to the hypotensive response, 13 patients obtained complete relief from their hypertensive or encephalopathic symptoms. Twelve additional patients had a moderate reduction and eight a slight reduction in symptoms. However, one patient (Case 17, Table 3) who was severely ill died after 18 hours of therapy, despite a satisfactory reduction in blood pressure. There was no evidence of coronary insufficiency despite the great reduction in blood pressure in this group of patients.

TOXIC REACTIONS

In the patients treated with "anatensol" orally, it was noted that the hypotensive dose closely approached the toxic dose. In the majority of patients (74%) toxic symptoms appeared before hypotension, necessitating discontinuance of the therapy. In addition, four of the eight patients (50%) having a hypotensive response had occasional nausea or vomiting during therapy. It is possible, however, that this difficulty could have been reduced with the use of the newer tablets [3] of "vergitryl" which have approximately one-half the therapeutic activity per milligram, since these would permit more careful titration of dosage. The difference between the toxic and the hypotensive oral dose of alkavervir was somewhat greater than the difference between the toxic and the hypotensive dose of "anatensol." However, even in this group 50% of the patients exhibited toxic symptoms requiring cessation of therapy before a hypotensive response could be obtained. Of the 15 patients in whom blood pressure was reduced, 6 patients (40%) had nausea and vomiting during therapy, and in another 2 nausea and vomiting occurred at the end of 13 and 52 weeks of treatment, at which time therapy had to be stopped. It was of interest that toxic reactions occurred less frequently in the patients receiving alkavervir intravenously than in those given alkavervir orally, in spite of the fact that blood pressure was reduced to a much lower level. Eight patients (21%) had nausea and vomiting, and another seven (18%) had severe nausea. In four patients (Cases 13, 14, 15, and 16, Table 3) therapy had to be discontinued because of toxic effects.

The most frequent toxic symptoms occurring with both oral and parenteral therapy were nausea and vomiting, as indicated in the text and shown in Tables 1, 2, and 3. However, other side-reactions were noted, these being chiefly hiccoughs, epigastric burning, weakness, faintness, and increased salivation. One patient had transient tinnitus and deafness and refused further therapy with "anatensol." (However, no studies were made to determine whether these were actually effects of the drug.)

COMMENT

Pharmacologic Aspects.—"Anatensol" and alkavervir are semipurified derivatives of Veratrum viride, containing several alkaloids. The active alkaloids responsible for their hypotensive effect have not been completely isolated, so far as is known to us. However, an incomplete preliminary report [5] lists the presence of the following active ester alkaloids in alkavervir in order of decreasing hypotensive effect per molecule [6]: germitrine, neogermitrine, germerine, protoveratrine, and alkaloid V-B.[7] In addition to these, germidine is another potent alkaloid which has been isolated from Veratrum viride.[8]

The pharmacologic effects of Veratrum viride and of many of the purified Veratrum alkaloids have been studied by several investigators in both animals [9] and man.[10] Their effects are a result of action on at least two different sites. The best known of these is the stimulatory effect on afferent vagal nerve endings in the region of the left ventricle of the heart and to a less extent in the lungs [11] (Fig. 2). They have also been shown to stimulate neuroreceptors in the carotid sinus area.[11e] As a result of stimulation of the afferent vagal nerve endings, impulses are transmitted centrally and returned via efferent vagal fibers to cause bradycardia. This effect can be blocked by atropine or vagotomy.[9a,e] Vasodepression also occurs from the

5. Riker Laboratories, Inc.: Personal communication to the authors.

6. Riker Laboratories, Inc.[5] Maison, G. L.; Gotz, E., and Stutzman, J. W.: The Hypotensive Potency of Pure Veratrum Alkaloids, J. Pharmacol. & Exper. Therap. **101**:24 (Jan.) 1951.

7. Scientific name to be designated later.

8. Freis, E. D.; Stanton, J. R., and Moister, F. C.: Chemical Fractions of Veratrum Viride and Identification of Pure Alkaloids, Germitrine, Germerine, and Germidine, J. Pharmacol. & Exper. Therap, **98**:166 (Feb.) 1950.

9. (*a*) Cramer, W.: On the Action of Veratrum Viride with Some Remarks on the Interrelationship of the Medullary Centers, J. Pharmacol. & Exper. Therap. **7**:63 (July) 1915. (*b*) Collins, R. J.: The Clinical Actions of Veratrum, Arch. Int. Med. **16**:54 (July) 1915. (*c*) Swiss, E. D.; Simon, H., and Stutzman, J. W.: Site of Cardiovascular Action of Hypotensive Veratrum Derivatives, Federation Proc. **10**:339 (March) 1951. (*d*) Dawes, G. S.: Studies on Veratrum Alkaloids: VI. Receptor Areas in the Coronary Arteries and Elsewhere as Revealed by the Use of Veratridine, J. Pharmacol. & Exper. Therap. **89**:325 (April) 1947. (*e*) Stutzman, J. W.; Simon, H., and Maison, G. L.: Role of Vagus Nerves in Depressor Action of Veratrum Derivatives, ibid. **101**:310 (March) 1951.

10. (*a*) Freis, E. D.; Stanton, J. R.; Culbertson, J. W.; Litter, J.; Halperin, M. H.; Burnett, C. H., and Wilkins, R. W.: The Hemodynamic Effects of Hypotensive Drugs in Man: I. Veratrum Viride, J. Clin. Invest. **28**:353 (March) 1949. (*b*) Wilkins, R. W.; Freis, E. D., and Stanton, J. R.: Essential Hypertension, J. A. M. A. **140**:261 (May 21) 1949. (*c*) Meilman, E., and Krayer, O.: Clinical Studies on the Pure Veratrum Alkaloids, Protoveratrine and Veratridine, J. Clin. Invest. **28**:798 (July) 1949.

11. (*a*) Cramer.[9a] (*b*) Dawes.[9d] (*c*) Krayer, O.; Wood, E. H., and Montes, D. G.: Studies on Veratrum Alkaloids: IV. The Sites of the Heart Rate Lowering Action of Veratridine, J. Pharmacol. & Exper. Therap. **79**:215 (Nov.) 1943.

action of Veratrum alkaloids on afferent vagus nerve endings. This reflex effect is not mediated through the same stimulatory efferent pathways as is the bradycardia, since it is not affected by atropinization.[9a,e] The Veratrum alkaloids also have a direct central action. This is independent of their stimulatory effect on the vagus, as has been shown by the following experiment: The head circulation of a dog was completely isolated from the remainder of the body and maintained by anastomosis to blood vessels of a second dog. The carotid sinuses were denervated, but other

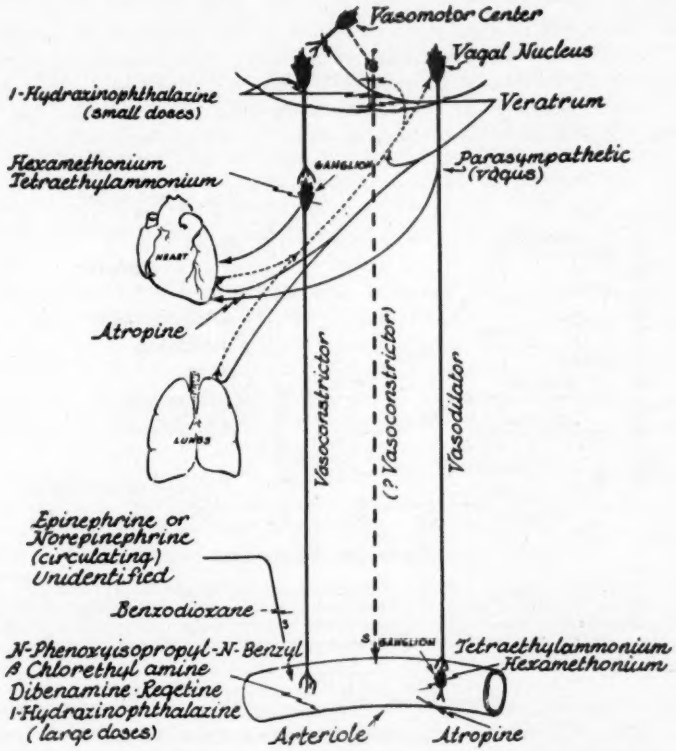

Fig. 2.—Diagrammatic representation of the autonomic nervous system indicating the site of action of some of the more important hypotensive agents. Veratrum acts by reflexly stimulating the vagus to cause reflex bradycardia and vasodepression. It also acts centrally, possibly blocking the outflow of vasoconstrictor impulses over unidentified vasoconstrictor neurogenic outflow tracts. Hexamethonium blocks the transmission of impulses through both sympathetic and parasympathetic ganglia. 1-Hydrazinophthalazine (hydralazine) has a central vasodepressor action, whereas N-phenoxyisopropyl-N-benzl-β-chlorethylamine ("dibenzyline"), "regitine" (phentolamine) and dibenamine® (N,N-dibenzyl-β-chlorethylamine hydrochloride) are peripherally acting sympatholytic drugs.

nerve pathways were left intact. The drug was then injected into the head circulation, and a hypotensive response without bradycardia was obtained in the body of the same dog. This was not altered by vagotomy or atropinization.[9c,e]

The efferent nervous pathway through which the vasodepressor response of Veratrum is mediated is not known. Sympathetic pathways are not thought to be involved, as sympathetic reflexes are still present (except for tachycardia) after its administration.[10a] In addition, high spinal blockade to the level of the fourth cervical vertebra does not eliminate the vasodepressor or cardiodecelerator action of veratrone® (a purified preparation of Veratrum viride).[12] It is, therefore, unlikely that their effect is mediated through known sympathetic nerve fibers. There does not seem to be any peripheral sympatholytic action, since administration of epinephrine or arterenol (nor-epinephrine) rapidly raises the blood pressure to pretreatment levels.[13] This is well demonstrated in Figure 1, as well as in the chart for a patient (Fig. 3) with a pheochromocytoma, proved at surgery. After an intravenous infusion of alkavervir, there was a decrease in blood pressure, followed by a sudden hypertensive crisis, apparently due to the sudden liberation of epinephrine. The vasodepressor response can be abolished or decreased by tetraethylammonium chloride [12]

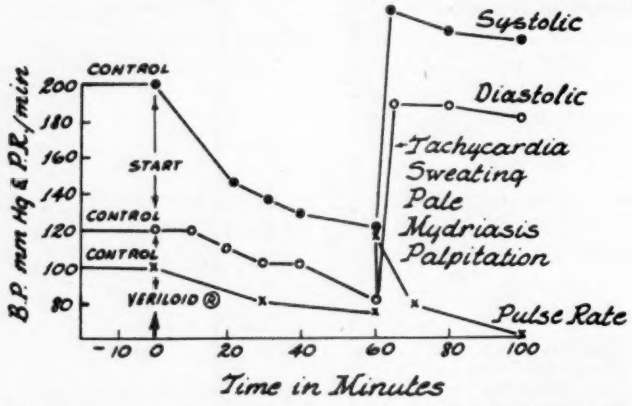

Fig. 3.—Response obtained following intravenous infusion of alkavervir (veriloid®) (0.5 γ per kilogram per minute × 20) in a patient with a pheochromocytoma (diagnosis proved at surgery). Following an initial drop in blood pressure, there was a sudden rise associated with tachycardia, sweating, and mydriasis. This was probably due to the sudden secretion of epinephrine by the tumor.

and other autonomic ganglionic blocking agents, which prevent transmission of impulses through sympathetic and parasympathetic ganglia. Since, as indicated previously, sympathetic pathways do not seem to be involved, the results with ganglionic blocking agents have led to the conclusion that Veratrum exerts its effect either through parasympathetic pathways not affected by atropine or other unidentified nervous pathways (designated by broken line in Figure 2).

Freis and associates [10a,b] have shown that cardiac output is unchanged or increased after the administration of Veratrum and that the decrease in blood pressure is due primarily to a decrease in peripheral resistance. There is an initial fall with return

12. Assali, N. S., and Prystowsky, H.: Studies on Autonomic Blockade: III. Effect of High Spinal Anesthesia on the Vasodepressor Action of Veratrum in Human Subjects, J. Pharmacol. & Exper. Therap. **100**:251 (Nov.) 1950.

13. Johnson and Mills.[4] Moyer, J. H.: Unpublished data.

to normal in splanchnic and renal blood flow, but glomerular filtration rate remains slightly depressed in some patients.[10a,b] Cerebral blood flow studies [14] in 10 hypertensive patients before and after reduction in blood pressure (mean blood pressure decreased from 173 to 108 mm. Hg) produced by intravenous administration of alkavervir showed a decrease in cerebrovascular resistance (mean blood pressure divided by cerebral blood flow) from 3.2 to 2.3, so that, in spite of the marked drop in blood pressure, there was only a slight decrease in cerebral blood flow, amounting to 7 ml. per 100 gm. of brain per minute.

The emetic effect of Veratrum derivatives is probably a central one and not a local one, as, at least with alkavervir, local gastric irritation is minimal.[15] The high incidence of nausea and vomiting in the patients in this series given alkavervir orally as contrasted with those given the drug intravenously was probably related to peaking of the drug level in the blood of the former, due to intermittent dosage rather than to the oral route. Large doses of Veratrum alkaloids apparently paralyze afferent vagal nerve endings and may have a stimulatory effect on the vasomotor and respiratory centers, leading to extreme tachycardia, hypertension, collapse, convulsions, cessation of respiration, and death.[9a,b] Recent studies have also shown that part of this effect may be associated with release of epinephrine from the adrenal medulla.[16]

Clinical Studies.—Our experience with "anatensol" and alkavervir was essentially in agreement with that of Barrow [17] and Wilkins [18] (Table 4). Twenty-six per cent of our 31 patients receiving "anatensol" had a blood-pressure response greater than 20/10, as compared with 16% of 25 patients treated by Barrow and co-workers.[17] In only one patient in the present series, however, did the average blood pressure fall below 140 systolic and 90 diastolic. Fifty per cent of our patients responded to alkavervir, as compared with 72% of 25 ambulatory patients reported on by Wilkins and associates.[18] In only one patient in each series (3 and 4%) did the blood pressure fall to normotensive levels. Results with other Veratrum preparations (vertavis®) [19] have been variable and range from 5 to 85% of patients having a reduction in blood-pressure response greater than 20/10.

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14. Moyer, J. H.; Miller, S. I.; Tashnek, A. B.; Snyder, H., and Bowman, R. O.: Cerebral Hemodynamic and Hypotensive Effect of Intravenous Veriloid Administered to Patients with Severe Hypertension and Hypertensive Encephalopathy, Am. J. Med., to be published.

15. Swiss, E. D.; Bain, R.; Maison, G. L., and Stutzman, J. W.: Locus of Emetic Action of Veriloid, J. Pharmacol. & Exper. Therap. **101**:35 (Jan.) 1951.

16. Krayer, O.; Moe, G. K., and Mendez, R.: Studies on Veratrum Alkaloids: VI. Protoveratrine; Its Comparative Toxicity and Its Circulatory Action, J. Pharmacol. & Exper. Therap. **82**:167 (Oct.) 1944.

17. Barrow, J. G., and Sikes, C. R.: The Use of Purified Veratrum Viride Alkaloids in the Treatment of Essential Hypertension, Am. Heart J. **41**:742 (May) 1951.

18. Wilkins, R. W.; Stanton, J. R., and Freis, E. D.: Essential Hypertension: Therapeutic Trial of Veriloid, a New Extract of Veratrum Viride, Proc. Soc. Exper. Biol. & Med. **72**:302 (Nov.) 1949.

19. (*a*) McNair, J. D.; Griffith, G. C., and Elek, S. R.: A Prolonged Study of Oral Veratrum Viride in the Treatment of Essential Hypertension, Am. Heart J. **40**:382 (Sept.) 1950. (*b*) Coe, W. S.; Best, M. M., and Kinsman, J. M.: Veratrum Viride in the Treatment of Hypertensive Vascular Disease, J. A. M. A. **143**:5 (May 6) 1950. (*c*) Josephs, I. L.: Therapy of Hypertension: Use of Veratrum Viride Alone and Combined with Certain Dihydrogenated Alkaloids of Ergot, Ann. West. Med. & Surg. **4**:789 (Dec.) 1950. (*d*) Freis, E. D., and Stanton, J. R.: A Clinical Evaluation of Veratrum Viride in the Treatment of Essential Hypertension, Am. Heart J. **36**:723 (Nov.) 1948.

When the effectiveness of Veratrum preparations in this series is evaluated over a one- to two-year period, the results are even less encouraging. Only two patients who received "anatensol" were able to continue taking the drug for this length of time (Cases 3 and 4, Table 1), and of the 30 patients originally receiving alkavervir, only 5 obtained continuing long-term therapeutic benefit.

Alkavervir given intravenously was found to be a very satisfactory hypotensive agent in the present study, when used on an acute basis, since 90% of the patients had a blood-pressure response greater than 40/20, and the remainder a response greater than 20/10. In 6 of 39 patients the average blood pressure was reduced to less than 140/90 after use of the drug. It must be noted, however, that a greater response could have been obtained by increasing the rate of infusion, and that the reported response was not necessarily the maximum tolerated one, but the amount of reduction which was felt to be safe for the patient.

TABLE 4.—*Comparison of the Hypotensive Effect of Extracts of Veratrum Viride*

Drug (Route)	Normotension (<140/90), %*	Response 40/20 or More, %	Response >20/10, but <40/20, %	Total >20/10, %	Average Daily Dose†	No. Patients
"Anatensol" (oral)	3	6	19	26	7.1 mg.	31‡
"Anatensol" (oral) [17]	0	0	16	16	3.9 mg.	25‡
Alkavervir (oral)	3	23	27	50	18.0 mg.	30‡
Alkavervir (oral) [18]	0	40	40	80	Acute	10§
	4	44	28	72	8 mg.	25‡
Alkavervir (oral); Gropper, A. L., and others, A. M. A. Arch. Int. Med. 87:789 (June) 1951	3	6	31	37	17.4 mg.	35§
	0	4	24	28	17.8 mg.	25‡
Alkavervir ((intravenous)	15	90	10	100	See text	39§
Vertavis® [19a]	0	0	5	5	82.3 Craw units	22‡
Vertavis® [19b,c]	0	0-4	12-76	12-80	10-83 Craw units	50
Vertavis® [19d]	0	67	17	83	55 Craw units	6§
	10	27	50	85	49.7 Craw units	34‡

* Per cent of patients with average blood pressure less than 140/90 during entire period after hypotensive response established.
† Average daily dose for entire group of patients.
‡ Ambulatory patients.
§ Hospitalized patients.

That the Veratrum preparations for oral use are relatively inefficient in comparison with some of the newer sympatholytic agents can be seen by comparison with the results obtained with hexamethonium chloride [20] and "dibenzyline" (N-phenoxyisopropyl-N-benzyl-β-chlorethylamine) [21] in the clinic in similar circumstances (Table 5).

Hexamethonium chloride is an agent which produces blockade of parasympathetic and sympathetic ganglia (Fig. 2). Both its hypotensive and its toxic effects are chiefly due to this action. Reduction of blood pressure in the erect position was obtained in 68% of patients treated. In the majority this was greater than 40/20, and in 28% normotensive levels were obtained. Reduction of the supine pressure was generally much less, but was usually significant with continued treatment.

20. Johnson, I.; Moyer, J. H.; Mills, L. C., and Miller, S. I.: Results with Hexamethonium Salts Administered Orally in the Treatment of Hypertension, Texas J. Med. **48**:331 (June) 1952.

21. Miller, S. I.; Moyer, J. H.; Ford, R. V., and Mills, L. C.: The Clinical Results with Dibenzyline in the Treatment of Hypertension and a Comparison of Results with Other Hypotensive Drugs, New England J. Med., to be published.

Long-term results cannot yet be given, but most of the patients reported on have been under treatment at least three to six months. Toxic effects were much less frequent than with Veratrum preparations and were chiefly due to parasympathetic blockade. They consisted mainly of nausea, constipation, occasional episodes of diarrhea, abdominal cramps, dry mouth, blurring of vision, and weakness.

"Dibenzyline" is a peripheral sympatholytic agent (Fig. 2) and, like hexamethonium, produces predominantly an orthostatic hypotension. The initial results in treatment of 32 hypertensive patients were very similar to those obtained with hexamethonium (Table 5). However, the incidence of toxic reaction was higher than with hexamethonium, but less than with alkavervir or "anatensol." These consisted chiefly of nausea, vomiting, weakness, tachycardia, and syncope. One other disadvantage of this drug is that there is no effective antidote for acute hypotensive reactions, should they occur, other than lying with the head slightly lowered. With

TABLE 5.—*Blood-Pressure Response to Veratrum Viride Compared with That Produced by Ganglionic and Adrenergic Blocking Agents*

Drug (Route)	Normotension (<140/90), %*	Response 40/20 or More, %	Response >20/10, but <40/20, %	Total >20/10, %	Average Daily Dose†	No. Patients
"Anatensol" (oral)	3	6	19	26	7.1 mg.	31‡
Alkavervir (oral)	3	23	27	50	18.0 mg.	30‡
Alkavervir (intravenous)	15	90	10	100	See text	39§
Hexamethonium [20] (oral; erect B. P.)	28	60	8	68	3.95 gm.	25‡
"Dibenzyline" ‖ [21] (oral; erect B. P.)	32	58	11	69	1.022 gm.	19§
	31	69	8	77	0.480 gm.	13‡
Hydralazine [22] (oral; erect B. P.)	8	15	23	38	490 mg.	13‡
Phentolamine ¶ [24] (oral; erect B. P.)	0	0	25	25	100-900 mg.	24‡
Phentolamine ¶ [24] (intravenous; erect B. P.)	88	94	6	100	1.3 mg./kg.	16§

* Percentage of patients with average blood pressure less than 140/90 during entire period after hypotensive response established.
† Average daily dose for entire group of patients.
‡ Ambulatory patients.
§ Hospitalized patients.
‖ N-phenoxyisopropyl-N-benzyl-β-chlorethylamine.
¶ "Regitine" (2-[N,p-tolyl-N-(m-hydroxyphenyl) aminomethyl] imidazoline hydrochloride).

hexamethonium, however, arterenol and ephedrine are rapidly effective in raising blood pressure.[13]

Blood-pressure reduction with hydralazine (1-hydrazinophthalazine) [22] alone was only slightly better than the response with "anatensol" and was less than that obtained with alkavervir given orally. This drug produces its hypotensive effects apparently through a central action (Fig. 2), although experimentally larger doses are associated with a peripheral sympatholytic effect. Here again orthostatic hypotension is prominent. Five of the patients had an initial blood-pressure response greater than 20/10, but only two were able to continue therapy as long as one year, and in one of these the blood pressure returned to control levels. The chief factor limiting its use was the high incidence of toxic side-reactions. These symptoms were anorexia, nausea, vomiting, tachycardia, severe palpitation, weakness, headache, nervousness, and, in some patients, anginal pains associated with electrocardiographic changes. Simultaneous administration of hexamethonium chloride, however, tended

22. Moyer, J. H., and Caplovitz, C.: Unpublished data.

to prevent these toxic effects, and in those patients who failed to respond to hexamethonium therapy alone, combination therapy sometimes led to a hypotensive response.[23]

Phentolamine ("regitine" [24], 2-[N,p'-tolyl-N-(m'-hydroxyphenyl) aminomethyl] imidazoline hydrochloride), a peripheral sympatholytic drug (Fig. 2), lowered blood pressure in 100% of the patients when given intravenously but is obviously impractical on a long-term basis. Phentolamine given orally lowered the blood pressure more than 20/10 in 25% of patients, but after three months of therapy failed to exert a hypotensive effect. Presumably, this was due to drug tolerance. The high incidence of toxic gastrointestinal effects (nausea, vomiting, and diarrhea) occurring with oral administration almost precluded its use by this route. Intramuscular and intravenous administration are associated with less frequent toxic effects, but the development of tachyphylaxis more or less limits its use to situations in which it is desirable to reduce blood pressure over short periods of time.

In comparison of the results of Veratrum therapy with those obtained with the use of ganglionic and adrenergic blocking agents, it must be noted that the latter drugs produced a greater hypotensive response in more patients. However, since their effect was predominantly an orthostatic one, there was only slight to moderate reduction in blood pressure when the patient was supine, whereas with the Veratrum alkaloids response, when it was obtained, was present in both the supine and the erect position.

CONCLUSIONS

It is apparent from the data presented that Veratrum preparations for oral administration have a definite hypotensive effect in some patients; however, it can also be seen that in a large percentage of patients this effect is minimal and that it is unlikely that the blood pressure will be reduced to normal levels. In addition, there is a very high incidence of associated toxic reactions which seriously limit the use of these preparations. From a practical point of view, one would not expect a decrease in pressure of only 20/10 to be of much benefit in the treatment of hypertension or in prevention of its complications. However, it may be worth while to give Veratrum preparations a therapeutic trial in hypertensive patients, since in the occasional patient in whom there is a moderate or marked vasodepression definite benefit may result. If the physician does elect to use this form of therapy initially, rather rapid therapeutic evaluation should be made. If the resulting hypotensive effect is inadequate, or if toxic symptoms are frequent, use of the drug should be discontinued and more promising therapeutic approaches tried. It would seem from this study and review of the literature that alkavervir is the available preparation of choice at present when oral Veratrum therapy is to be used. However, careful attention must be given to dosage during the titration and subsequent maintenance periods in order to secure optimal results. In the future, it may be possible to give pure preparations of a single alkaloid, such as protoveratrine, which may have greater hypotensive properties with fewer toxic effects.[10c]

There is one other indication for use of Veratrum in hypertension. This is in the treatment of hypertensive crises and encephalopathy, on a short-term basis, with alkavervir by continuous infusion. Intravenously, it is very effective, and we have

23. Moyer, J. H.; Mills, L. C.; Johnson, I., and Miller, S. I.: Unpublished data.

24. Moyer, J. H.; Caplovitz, C., and Handley, C. A.: Unpublished data.

not yet seen a patient who failed to respond, although in a few toxic manifestations prevented its use for more than 18 to 24 hours. It has been very effective in relieving the symptoms of a hypertensive crisis and may be given for days. It is very important when using the drug intravenously that proper precautions be taken for possible excessive administration. An infusion containing 4 γ of arterenol per milliliter should be prepared beforehand for immediate administration should the blood pressure decrease excessively at any time.

The data presented indicate that hexamethonium is the most effective drug for oral use in prolonged therapy of hypertension, when degree of response, number of patients responding, and incidence of toxic symptoms are considered.

SUMMARY

Of 31 ambulatory patients given "anatensol" (an extract of Veratum viride) in an average daily dose of 7.1 mg. per day, 26% had a fall in blood pressure greater than 20/10, and in 1 patient normotensive levels were obtained. Its therapeutic index was very low.

Of 30 patients treated with an average daily dose of alkavervir (veriloid®) of 18 mg. per day, 50% had a hypotensive response greater than 20/10, but only in 1 of the 30 patients could the blood pressure be reduced to normotensive levels. Its therapeutic index was also low.

There was a fall in blood pressure greater than 20/10 in all 39 patients given alkavervir intravenously by continuous infusion. In 17 patients this effect was maintained for an average of 55 hours.

The therapeutic indications for Veratrum therapy are discussed, and the results obtained are compared with those of other investigators using Veratrum preparations. In addition, the effectiveness and toxicity of Veratrum preparations are compared with those of some of the newer ganglionic and adrenergic blocking agents.

Hexamethonium appears to be the best single drug in the long-term oral treatment of hypertension and alkavervir administered intravenously the most satisfactory drug for short-term reduction of blood pressure in hypertensive crises.

ERRONEOUS ANEMIA AND POLYCYTHEMIA

A Comparative Study of Peripheral Blood and Blood Volume

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THE PHENOMENA of erroneous anemia and polycythemia as related to blood volume have been given little attention. The red cell mass and circulating hemoglobin may be entirely normal in a person in whom the peripheral blood elements and hemoglobin concentration are below the accepted normal values. Pseudopolycythemia may be caused by a decreased plasma volume. Even in polycythemia vera there may be a lack of correlation between the peripheral blood and the blood volume.

This report presents the results of simultaneous studies of the peripheral blood and blood volume in 62 human subjects, 13 with "anemia of neurasthenia," 17 with a decreased plasma volume, 17 with normal and pathologic pregnancy, and 15 with polycythemia vera.

METHODS

Blood volume and peripheral blood studies were done simultaneously so that the results could be correlated. The hemoglobin concentration was determined by the oxyhemoglobin method of Sheard and Sanford,[1] using a Coleman Junior spectrophotometer. The standards were checked by a spectrophotometric adaptation for whole blood iron after the methods of Wong,[2] Dupray,[3] Walker and Fitz,[4] and Ponder.[5] The calibration of the machine was also checked each seven days by oxygen capacity, based on the methods of Exton, Schattner, and Rose [6] and Exton,

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Schattner, Korman, and Rose.[7] The blood volume studies were done by Gregersen's modification[8] of the method of Gibson and Evans,[9] using Evans blue dye T-1824 and the Coleman Junior spectrophotometer with constant voltage control. Certain precautions were taken. Evans blue dye was purchased in lots and carefully standardized by determining the optical density of a 1:500 dilution of the dye in normal dye-free plasma. Because of the opaque solution obscuring the plunger head, all syringes were calibrated by filling with a standard acid and titrating a delivered volume with a standard base. After the intravenous injection of the dye, the blood specimens for calibration of blood volume were obtained from the opposite antecubital vein. At first blood specimens were obtained at 4, 10, 15, and 30 minutes. Inasmuch as the patients in this series were not in shock and there was no impairment of the circulation, a single specimen obtained 10 minutes after injection of the dye was found to be adequate for complete and thorough mixing.[8] A clear serum control was used as the reference blank for setting the spectrophotometer at 620 mμ at 0 optical density. The optical density of the dye-tinged serum was then observed. Lipemic and hemolyzed specimens were discarded. The hematocrit determinations were done by the method of Wintrobe.[10] The accepted normal values for erythrocytes and hemoglobin concentration for normal adults were those given by Wintrobe[10]: females, 4.8±0.6 erythrocytes (million per cubic millimeter) and 14 gm. ±2.0 hemoglobin per 100 cc.; males, 5.4±0.8 erythrocytes (million per cubic millimeter) and 16 gm. ±2.0 hemoglobin per 100 cc.

RESULTS

"Anemia of Neurasthenia."—This type of anemia has been thoroughly described by Dameshek[11] and is represented by the neurasthenic women with moderate normocytic normochromic anemia which does not respond to any type of antianemic therapy. Nervousness, anxiety, tension, and fatigue dominated the clinical picture in our patients and were out of proportion to the general appearance of good health. Results of physical examinations were essentially normal. The basal metabolic rates or results of radioactive iodine (I^{131})-uptake studies were within normal limits. In eight subjects the dextrose-tolerance curve was of the flat type so frequently seen in this type of patient.[12]

In all these 13 patients the peripheral blood studies revealed values for hemoglobin concentration and erythrocytes below the accepted levels of normal (Chart 1). Blood volume observations, as related to body weight, revealed that the circulating red cell mass in each patient was within the limits of normal, only two showing values below the mean average, but within the accepted range of normality.

Decreased Plasma Volume.—Observations were obtained on 15 white male and two white female subjects in whom the plasma volume was decreased (Chart 2). An erroneous increase in the peripheral hemoglobin and erythrocyte levels occurred in six subjects. Two brothers (14th and 15th from left, Chart 2) had cerebellar

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8. Gregersen, M. I.: Practical Method for Determination of Blood Volume with Dye T-1824: Survey of Present Basis of Dye-Method and Its Clinical Applications, J. Lab. & Clin. Med. **29**:1266, 1944.

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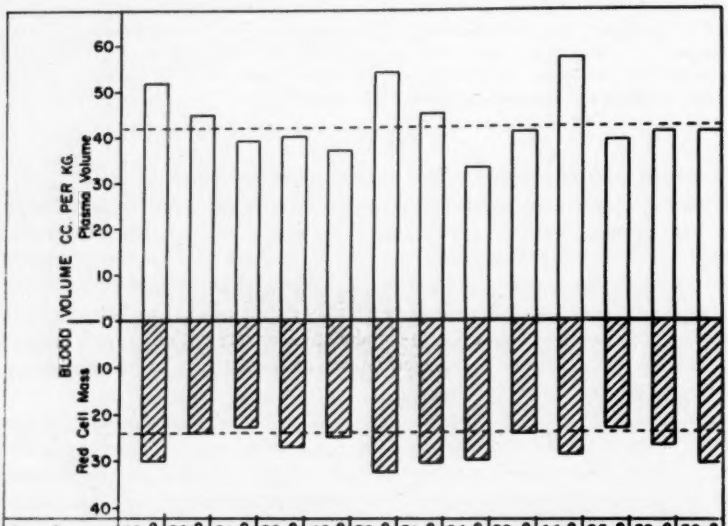
11. Dameshek, W.: Anemia of Neurasthenia, editorial, Blood **2**:485, 1947.

12. Portis, S. A.: Mechanism of Fatigue in Neuropsychiatric Patients, J. A. M. A. **121**:569, 1943; The Medical Treatment of Psychosomatic Disturbances with Special Reference to Gastrointestinal Tract and Fatigue, ibid. **126**:413, 1944. Alexander, F., and Portis, S. A.: A Psychosomatic Study of Hypoglycemic Fatigue, Psychosom. Med. **6**:19, 1944.

hemangioblastomas, one having an actual polycythemic red cell mass and the other essentially normal values. One patient (13th from left, Chart 2) had emphysema, and the red cell mass was elevated above the limits of normality. The remaining seven were normal subjects. Seven of the patients were referred to the hematologic clinic with a diagnosis of polycythemia, and six had been treated by phlebotomy.

In all these subjects the peripheral blood levels of hemoglobin and erythrocytes were modified, at times markedly, by the decreased plasma volume. Thus, a concentration phenomenon occurred in all but one subject with false elevated levels of hemoglobin and erythrocytes. In the remaining patient (third from left, Chart 2), the red cell mass was also decreased below the accepted limits of normal.

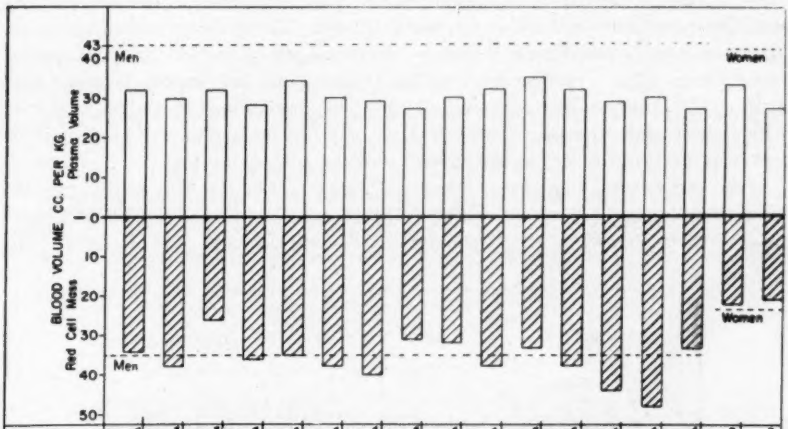


Age, Sex	25 ♀	30 ♀	61 ♀	50 ♀	40 ♀	59 ♀	31 ♀	64 ♀	52 ♀	44 ♀	55 ♀	52 ♀	56 ♀
RBC Mm. 3	3.78	3.76	3.60	3.61	3.25	3.60	3.61	4.10	4.00	3.43	3.80	3.75	4.00
Hb Gm. %	10.0	10.0	10.5	9.7	10.1	11.0	11.2	10.8	10.5	9.7	9.5	10.9	11.5
Hemat. cc. %	36.0	35.0	37.0	40.5	40.0	40.0	40	45.0	36.5	34	37	38	42

Chart 1.—Compiled data on 13 cases of "anemia of neurasthenia." Although erythrocyte count (red blood cells, millions per cubic millimeter) and hemoglobin concentration are below accepted normal values, red cell mass is within normal limits. No true anemia exists. Dotted lines indicate average normal values.

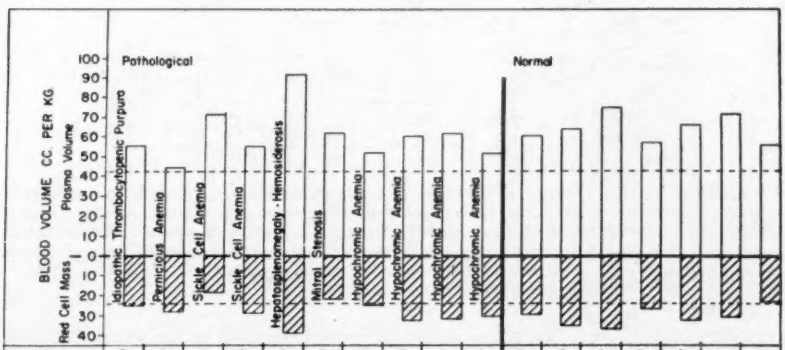
Pregnancy.—Seventeen pregnant patients were observed for whom a diagnosis of anemia had been made (Chart 3). All were white, with the exception of two with sickle-cell anemia. Seven of these patients were entirely normal, the only "defect" being a normal physiologic increase in the red cell mass, which was diluted by a normal pregancy increase in the plasma volume.

Nine of the patients had some type of hematologic disease. One patient with thrombocytopenic purpura had a splenectomy during her seventh month of pregnancy with an excellent result. The baby was born at term with temporary thrombocytopenia. The studies on the patient with pernicious anemia were entirely normal, and



Age, Sex	50 ♂	58 ♂	46 ♂	56 ♂	22 ♂	47 ♂	27 ♂	34 ♂	48 ♂	42 ♂	69 ♂	64 ♂	53 ♂	15 ♂	22 ♂	33 ♀	58 ♀
RBC Mm. 3	5.12	6.0	5.0	5.51	5.69	6.2	6.0	5.4	5.7	6.0	5.37	5.7	7.26	6.65	5.56	4.27	4.9
Hb. Gm. %	15.9	17.0	11.2	17.1	16.0	18.6	18.4	16.2	17.0	15.4	15.0	17.0	15.7	17.5	14.2	11.5	13.5
Hemat. cc. %	51	58	44.0	55.5	51.0	55.0	57.5	53.0	52.0	53	50.0	53	60	60	55	40	44.2
Phlebotomy	0	0	+	0	0	+	0	0	0	+	+	0	+	0	0	0	+
Plasma Decr. %	26	31	26	35	21	31	33	37	31	26	19	24	33	31	37	22	36

Chart 2.—Compiled data on 17 subjects with decreased plasma volume. Thirteenth and 14th patients (from left) are moderately polycythemic. Third patient had been subjected to numerous phlebotomies. Remainder each have red cell mass within normal limits. For six subjects diagnosis of polycythemia vera had been made, and they were treated by phlebotomy.

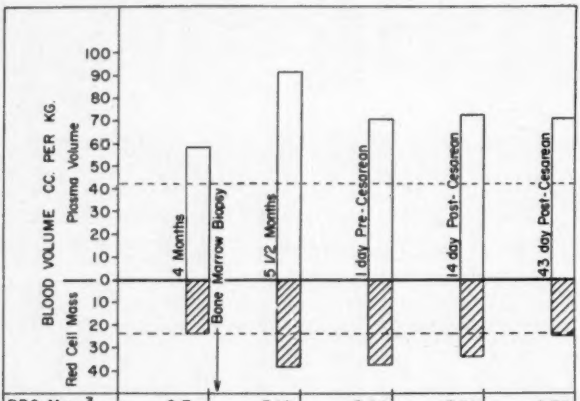


Mo. of Pregnancy	7	5	6	5	6	5	9	6	8	8	5	7	8	5	5	9	9
Age - years	31	24	38	30	29	37	27	33	29	28	30	41	42	34	31	37	32
RBC Mm. 3	3 6	3 54	1 26	3 7	3 8	2 66	3 4	4 02	4 25	3 90	2 6	3 3	3 4	3 27	3 59	2 38	3 00
Hb Gm %	9 3	10 5	4 6	9 2	7 6	6 6	8 1	8 6	8 5	9 9	9 3	10 0	9 8	8 4	9 8	6 6	8 6
Hemat cc %	32	39	21	32	30	28	32	35	30 5	38	33	37 0	40 5	32	33	33	28
Plasma Incr %	31	0	69	47	116	31	21	43	43	21	43	50	78	36	57	71	33

Chart 3.—Compiled data on 10 women with pathologic pregnancies and 7 with normal pregnancies. Degree of true anemia is not so severe as peripheral blood studies would indicate, erythrocytes being "diluted" by increased plasma. "Anemia" in normal pregnant subject is not absolute but relative, hydremia being obvious.

she had only a minimal hydremia during her entire pregnancy. The two patients with sickle-cell anemia were of interest in that the blood volume studies gave us assurance that the anemia was not as severe as one would conclude from peripheral blood values alone. The patient with the severer sickle-cell anemia delivered normally. The other has not delivered as yet. The observations on the four patients with hypochromic anemia revealed that the red cell mass was increased in three instances and the circulating hemoglobin was also at least normal.

One patient was of particular interest (Chart 4). She was first seen during the fourth month of pregnancy with slight skin pigmentation, splenomegaly, and hepatomegaly. The peripheral blood count revealed reticulocytosis and moderate pan-



RBC Mm. 3	2.7	3.18	3.44	3.21	2.79
Hb. Gm. %	7.5	7.6	9.4	9.9	7.6
Hemat. cc. %	30	30	35	31	26.5
Platelets	144	218	—	—	219
Reticulocytes %	7.0	6.2	—	—	8.8
Icterus Index u.	4.5	24	16.5	—	—
Plasma Incr. %	38	116	66	71	66

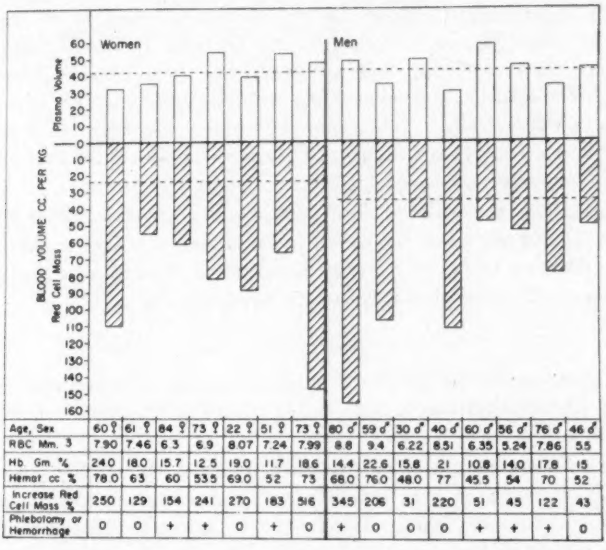
Chart 4.—For this pregnant patient (H. S., a white woman aged 29 years) a preliminary diagnosis was made of secondary hypersplenism due to hepatosplenomegaly caused by hemosiderosis, and splenectomy was recommended. Moderate pancytopenia existed. Blood volume study revealed a plasma increase causing false anemia, and operation was not done. Red cell mass was either normal or increased throughout entire period of observation. Platelets (thrombocytes) are expressed in thousands per cubic millimeter.

cytopenia, a decrease being noted in all the formed elements of the blood. A bone marrow biopsy revealed a hyperplasia of the erythroid, neutrophilic, and megakaryocytic cells. Numerous liver-function tests disclosed only minimal differences from normality. The dextrose-tolerance curve was within normal limits. A diagnosis of early hemosiderosis was made by liver biopsy. It was concluded that the patient had secondary hypersplenism, and an immediate splenectomy was advised. However, a blood volume determination was first obtained, with the result that the plans for splenectomy were immediately canceled. The red cell mass was entirely normal, the peripheral erythrocyte and hemoglobin values being distorted by an increase in plasma volume. Observations at five and one-half months and one day before

Cesarean section revealed a further increase in these values. The red cell mass returned to normal by the 43d post-Cesarean day, the plasma volume remaining elevated. Thus, the final diagnosis was hydremia and not hypersplenism. A splenectomy was definitely contraindicated.

Polycythemia Vera.—Although many patients were observed, only 15 were selected to illustrate the lack of correlation between peripheral blood levels and blood volume. Seven were white women and eight were white men (Chart 5).

In five subjects there was a significant decrease in the plasma volume which further concentrated the red cell mass, giving higher values for hemoglobin, erythrocytes, and hematocrit. An excellent example of the lack of correlation is provided



Age, Sex	60 ♀	61 ♀	84 ♀	73 ♀	22 ♀	51 ♀	73 ♀	80 ♂	59 ♂	30 ♂	40 ♂	60 ♂	36 ♂	76 ♂	46 ♂
RBC Mm. 3	7.90	7.46	6.3	6.9	8.07	7.24	7.99	8.8	9.4	6.22	8.51	6.35	5.24	7.86	5.5
Hb. Gm. %	24.0	18.0	15.7	12.5	19.0	11.7	18.6	14.4	22.6	15.8	21	10.8	14.0	17.8	15
Hemat cc %	78.0	63	60	53.5	69.0	52	73	68.0	76.0	48.0	77	45.5	54	70	52
Increase Red Cell Mass %	250	129	154	241	270	183	516	345	206	31	220	51	45	122	43
Phlebotomy or Hemorrhage	0	0	+	+	0	+	0	+	0	0	0	+	+	+	0

Chart 5.—Summary of data on 15 cases of polycythemia vera. Peripheral blood studies actually do not give desired data concerning increase in red cell mass. Hemoglobin, erythrocytes, and hematocrit, as determined by peripheral blood studies, may be concentrated in some subjects by a decrease in plasma volume.

by the data on the first woman and the first man in Chart 5. The hematocrit is higher in the former, though the red cell mass per kilogram of body weight is less. Because of phlebotomy and the production of a relative hypochromia and microcytosis, the red cell count could not be used as an index of the red cell mass. The hematocrit was also a poor index, but when correlated with the hemoglobin concentration it gave us more information about the patient's status in regard to the results of phlebotomy than any of the other peripheral blood factors. The first man in Chart 5 is an example of how a patient may not be under good control by phlebotomy. The hemoglobin concentration was decreased and the hematocrit markedly elevated. Continued phlebotomy was not desirable and radioactive phosphorus was used.

COMMENT

As has been previously stated, scant attention has been given to the effect of the plasma volume and the red cell mass on changes in the peripheral blood. Tysoe and Lowenstein [13] reported their observations on blood volume and hematologic studies in pregnancy and the puerperium and found that, even though peripheral blood values might be decreased, the circulating hemoglobin concentration and red cell mass rose, being diluted by an increased plasma volume. Previous investigators have reported on the increased plasma volume during pregnancy.[14]

The changes in blood volume in various diseases have been studied by Erlanger [15] and Rowntree, Brown, and Roth.[16] In chronic secondary anemia there was a reduction in the volume of the blood and cells according to body weight and body surface. In splenomegaly with anemia and in hemolytic anemia the anemia was found to be actual, although accentuated by dilution. In anemia the published results have been conflicting, but in general the total blood volume is little reduced.[17] The total blood volume in leukemia is elevated because of an increase in plasma as well as cells.[10] The same phenomenon has been reported in other conditions in which the spleen is enlarged, such as cirrhosis of the liver and Banti's syndrome (congestive splenomegaly).[10]

No conclusions should be reached from minor changes in either the plasma volume or the red cell mass. However, it would seem from the studies presented that more attention should be given to simultaneous blood volume and peripheral blood studies in the borderline anemias and polycythemias.

CONCLUSIONS

A comparative study of peripheral blood levels of erythrocytes and hemoglobin and blood volume in relation to body weight in 62 human subjects revealed a lack of correlation in many instances.

In the so-called anemia of neurasthenia, in which the erythrocyte count and hemoglobin concentration were below the accepted normal standards, the red cell mass was within normal limits. Their notorious failure to respond to antianemic therapy is not surprising.

13. Tysoe, R. W., and Lowenstein, L.: Blood Volume and Hematologic Studies in Pregnancy and Puerperium, Am. J. Obst. & Gynec. **60**:1187, 1950.

14. Dieckmann, W. J., and Wegner, C. R.: Studies of Blood in Normal Pregnancy: I. Blood and Plasma Volumes, Arch. Int. Med. **53**:71, 1934. Thomson, K. J.; Hirsheimer, A.; Gibson, J. G., and Evans, W. A., Sr.: Studies on Circulation in Pregnancy: III. Blood Volume Changes in Normal Pregnant Women, Am. J. Obst. & Gynec. **36**:48, 1939. Caton, W. L.; Roby, C. C.; Reid, D. E., and Gibson, J. G.: Plasma Volume and Extravascular Fluid Volume During Pregnancy and Puerperium, ibid. **57**:471, 1949.

15. Erlanger, J.: Blood Volume and Its Regulation, Physiol. Rev. **1**:177, 1921.

16. Rowntree, L. G.; Brown, G. E., and Roth, G. M.: The Volume of Blood and Plasma in Health and Disease, Philadelphia, W. B. Saunders Company, 1929.

17. Gibson, J. G.; Harris, A. W., and Swigert, V. W.: Macrocytic and Hypochromic Anemias Due to Chronic Blood Loss, Hemolysis, and Miscellaneous Causes, and Polycythemia Vera, J. Clin. Invest. **18**:621, 1939.

A decrease in the plasma volume may cause the peripheral blood levels erroneously to appear polycythemic. For six subjects with decreased plasma volume, a diagnosis of polycythemia had been made, and they had been treated by phlebotomy.

An anemia occurring in pregnancy can be completely evaluated only by a comparative study of the peripheral blood and blood volume. The patient may not be anemic, and the decreased peripheral hemoglobin and erythrocyte levels may be caused by a physiologic increase in plasma volume. In pregnancy complicated by true anemia, the degree of the anemia may not be as severe as one would conclude from peripheral blood studies alone.

In polycythemia vera the red cells may be concentrated by a decreased plasma volume. The peripheral blood levels of red cells, hemoglobin, and hematocrit give no indication of the total blood volume and red cell mass.

PAGET'S DISEASE (OSTEITIS DEFORMANS)

Review of One Hundred Eleven Cases

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PAGET'S disease of bone (osteitis deformans) was described in the latter part of the 19th century, although it probably existed in ancient times. Butlin [1] believed that the Neanderthal skull had the lesions of osteitis deformans. Denninger [2] reported the characteristic bone changes of this disease among American Indian skeletons excavated in the region of the Illinois River Valley; Fisher [3] unearthed a pair of tibiae with the bone changes of osteitis deformans in the village of Lynxville in Crawford County, Wisconsin. In 1873 Czerny [4] named the disease osteitis deformans, but it was Paget [5] who correlated and described the clinical and pathological features. In his first report in 1876 he analyzed the cases reported by Urany in 1867 and Wilks in 1869 and added several of his own. In two later papers [6] he reviewed data on 23 patients. Since then, the medical profession has applied the name "Paget's disease of bone" to the clinical entity. Though some of Paget's original theories were disproved, many of his observations remain unchanged today. During the years 1922 to 1926, investigators culled several hundred cases from the literature.[7] From then until the present, various aspects of this disease have been the subject of many discussions. Despite this wealth of literature, the causation and the treatment of the disorder remain uncertain.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Butlin, H. T.: Pathological Reports on Osteitis Deformans, Lancet **1**:519 (March) 1885.

2. Denninger, H. S.: Paleopathological Evidence of Paget's Disease, Ann. M. Hist. **5**:73 (Jan.) 1933.

3. Fisher, A. K.: Additional Paleopathological Evidence of Paget's Disease, Ann. M. Hist. **7**:197 (March) 1935.

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6. (*a*) Paget, J.: Additional Cases of Osteitis Deformans, Med.-Chir. Tr., London **65**:225, 1882; (*b*) Remarks on Osteitis Deformans, Illus. M. News **2**:181, 1889.

7. (*a*) Goldstein, H. I.: Paget's Disease of Bones, M. Times, New York **50**:279 and 321, 1922; **52**:56, 1924; **54**:194, 1926. (*b*) Roberts, R. E., and Cohen, M. J.: Osteitis Deformans (Paget's Disease of Bone), Proc. Roy. Soc. Med. (Section of Electro-Therapy) **19**:13 (March) 1926.

The present study is based on a review of the clinical records of 111 patients with Paget's disease of bone who were admitted to the Veterans Administration Hospital, Bronx, N. Y., between 1941 and 1950. A number of these patients were reexamined, while others were requested to complete questionnaires. Not all the 111 patients could be contacted, so that we were unable to obtain complete information for each element tabulated.

INCIDENCE

Paget's disease of bone is often an unexpected finding in the course of a variety of roentgenologic examinations. It is obvious that one cannot compare the incidence of this disease as it is found in a general hospital with that reported in specialized orthopedic or rheumatic disease hospitals, where more complete skeletal surveys are performed. Incidence has been reported[8] as ranging from 1 in 170 to 1 in 15,000 admissions. The higher rates of 1 in 170 to 1 in 400 were obtained in those hospitals in which the largest numbers of roentgen studies on admission are performed, in specialized hospitals for bone or rheumatic diseases, and when the incidence was calculated on the basis of postmortem studies.[9] At this hospital the diagnosis of Paget's disease of bone was made 111 times in 94,112 admissions (1:850). This is a high incidence for a general hospital, but it may be explained by our careful reading of large numbers of roentgenograms. Apparently the true incidence of osteitis deformans may be higher when detailed skeletal surveys are made of the older population.

CAUSATION

Since Paget's initial description medical writers have speculated about the causation of this bone affliction. The causative factor is still elusive. Chronic inflammation,[10] syphilis,[11] toxic irritation with disturbed metabolism,[12] and dis-

8. (*a*) Summey, T. J. and Pressly, C. L.: Sarcoma Complicating Paget's Disease of Bone, Ann. Surg. **123**:135 (Jan.) 1946. (*b*) Campbell, E., and Whitfield, R. D.: Osteogenic Sarcoma of Vertebrae Secondary to Paget's Disease: Report of 3 Cases with Compression of Spinal Cord and Cauda Equina, New York J. Med. **43**:931 (May 15) 1943. (*c*) Bird, C. E.: Sarcoma Complicating Paget's Disease of the Bone: Report of 9 Cases, 5 with Pathologic Verification, Arch. Surg. **14**:1187 (June) 1927. (*d*) Hurwitz, S. H.: Osteitis Deformans, Paget's Disease: A Report of 6 Cases, Bull. Johns Hopkins Hosp. **24**:263 (Sept.) 1913. (*e*) Packard, F. A.; Steele, J. D., and Kirkbridge, J. S.: Osteitis Deformans, Am. J. M. Sc. **122**:252 (Nov.) 1901. (*f*) Codman, E. A.: Registry of Bone Sarcoma, Surg., Gynec. & Obst. **42**:381 (March) 1926. (*g*) Coley, B. L., and Sharp, G. S.: Paget's Disease: A Predisposing Factor to Osteogenic Sarcoma, Arch. Surg. **23**:918 (Dec.) 1931. (*h*) Da Costa, J. C.; Funk, E. H.; Bergeim, O., and Hawk, P. B.: Osteitis Deformans: A Report of 5 Cases with Complete Metabolism Studies in 2 Instances and a Review of the Literature, Pub. Jefferson M. Coll. & Hosp. **6**:1, 1915. (*i*) Abel, W., and Hellwegen, F.: Sarkom auf dem Boden einer Ostitis deformans Paget, Röntgenpraxis **10**:93 (Feb.) 1938. (*j*) O'Reilly, T. J., and Race, J.: Osteitis Deformans, Quart. J. Med. **1**:471 (Oct.) 1932. (*k*) Schmorl, G.: Über Ostitis deformans Paget, Arch. path. Anat. **283**:694, 1932.

9. Bird.[8c] Footnote 8*i* to *k*.

10. Paget.[5] Da Costa and others.[8h]

11. (*a*) Lannelongue, O., cited by Da Costa and others.[8h] (*b*) Fournier, M.: À propos de la maladie de Paget considérée comme manifestation de syphilis héréditaire tardive, Bull. méd., Paris **17**:301, 1903.

12. Knaggs, R. L.: On Osteitis Deformans (Paget's Disease) and Its Relation to Osteitis Fibrosa and Osteomalacia, Brit. J. Surg. **13**:206 (Oct.) 1925; The Inflammatory and Toxic Diseases of Bone: A Text-Book for Senior Students, New York, William Wood & Company, 1926, pp. 289-329.

turbed endocrine function affecting bone metabolism [6b] have been indicted. Paget's original concept of chronic inflammation has been abandoned. Syphilis may be dismissed as a causative factor since the incidence of syphilis among patients with Paget's disease ranges from 3 to 8%.[13]

Because the causation of osteitis deformans is unknown, the literature concerned with certain phases of bone physiology and of related metabolic factors was searched in an effort to shed some light on this elusive problem. Some of the highlights of this review are summarized:

This much is known about the growth hormone[14]: It brings about marked retention of nitrogen and impairs carbohydrate utilization in fed animals. The administration of this hormone prevents the loss of muscle glycogen in fasted hypophysectomized animals. It causes a diminution in the uptake of glucose by the isolated diaphragm. In normal fed rats or in fasted hypophysectomized rats growth hormone depresses the respiratory quotient (R. Q.), and in alloxan-induced diabetes and in partially depancreatized rats it exaggerates the diabetic state. The administration of growth hormone to dogs, cats, rats, and batrachians establishes a permanent diabetes.[15]

Recent reports demonstrate the role of alkaline phosphatase in the synthesis of fibrous protein and its activity upon the cartilage matrix in calcification.[16] Alkaline phosphatase is, therefore, essential to bone formation and also plays a part in bone regeneration.[17] It is not surprising then that serum and bone alkaline phosphatase are elevated in the process of body and bone growth.[18] The effect on serum alkaline

13. (*a*) Gutman, A. B., and Kasabach, H.: Paget's Disease (Osteitis Deformans): Analysis of 116 Cases, Am. J. M. Sc. **191**:361 (March) 1936. (*b*) Dickson, D. D.; Camp, J. D., and Ghormley, R. K.: Osteitis Deformans (Paget's Disease of Bone), Radiology **44**:449 (May) 1945.

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15. Marx, W.; Anderson, E.; Fong, C. T. O., and Evans, H. M.: Effects of Growth Hormone on Glycosuria of Fed Partially Depancreatized Rats, Proc. Soc. Exper. Biol. & Med. **53**:38 (May) 1943. Houssay, B. A.: La accion diabetogena de la hipofisis, Thesis, Buenos Aires, 1945. Houssay, B. A., and Anderson, E.: Diabetogenic Action of Purified Anterior Pituitary Hormones, Endocrinology **43**:627 (Dec.) 1949. Cotes, P. M.; Reid, E., and Young, F. G.: The Diabetogenic Action of Pure Anterior Pituitary Growth Hormone, Nature, London **164**:209 (Aug. 6) 1949. Campbell, J.; Davidson, I. W. F.; Snair, W. D., and Lei, H. P.: Diabetogenic Effect of Purified Growth Hormone, Endocrinology **46**:273 (March) 1950.

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phosphatase by several of the known hormones has been studied. Testosterone propionate [19] raises alkaline phosphatase. Adrenalectomy [20] lowers alkaline phosphatase in a cat kidney. Desoxycorticosterone [21] is without influence on serum alkaline phosphatase. Lactogenic hormone has no effect upon alkaline phosphatase.[22] Hypophysectomy [23] causes a decrease in alkaline phosphatase, probably through the adrenal glands. Anterior pituitary growth hormone stimulates bone growth [24] and increases tibial weight, with a rise in alkaline phosphatase.[25] Growth hormone probably stimulates osteoblastic activity with a secondary rise in alkaline phosphatase. Corticotropin (ACTH) has an inhibiting effect on the growth of young and adult male rats [26] and on serum alkaline phosphatase. Boom [27] and Pond [28] have described cases of Paget's disease associated with pituitary lesions. Corticotropin, cortisone, or adrenocortical extracts will cause existing elevated serum alkaline phosphatase in human beings and in animals to decline; normal alkaline phosphatase levels remain relatively unaffected.[29] When corticotropin

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27. Boom, H.: Simmonds' Pituitary Cachexia Associated with Osteitis Deformans, Nederl. tijdschr. geneesk. **80**:3336 (July 19) 1936.

28. Pond, C. W.: Paget's Disease: Pituitary Tumor and Absence of Sphenoid Sinus; Report of Case, Ann. Otol. Rhin. & Laryng. **49**:500 (June) 1940.

29. (*a*) Watson.[21] (*b*) Li and others.[22] (*c*) Li and others.[23b] (*d*) Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R. Jr.; Roche, M.; Staehelin, D. S., and Wilson, D. L.: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:865 (June 1); 783 (May 18); 824 (May 25) 1950. (*e*) Bardawill, C. J.; Gornall, A. G.; Nishikawara, M., and Wightman, K. J. R.: Studies on the Behavior of Urinary Amino Nitrogen, Serum Alkaline Phosphatase, and Pseudocholinesterase Activity During ACTH Therapy, in Proceedings of the Second Clinical ACTH Conference, Vol. I: Research, edited by J. R. Mote,

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and growth hormone are administered simultaneously they counteract each other with respect to the effect on alkaline phosphatase levels.[30] It is evident, therefore, that in order to maintain a normal blood and bone alkaline phosphatase the various fractions of the anterior pituitary must be in sensitive balance.

Investigators [31] have demonstrated impaired dextrose tolerance in osteitis deformans. Apperly and Cary [32] feel that abnormal dextrose-tolerance curves found in their patients with Paget's disease are compatible with hyperpituitarism and suggest that the skull changes may affect the pituitary fossa. The anterior pituitary gland has a direct influence on carbohydrate metabolism. The administration of anterior pituitary extract in the presence of intact adrenal cortex produces diabetes. Anterior pituitary extract inhibits hexokinase. After hypophysectomy, animals are more sensitive to insulin.[33] Moreover, growth hormone is a second known diabetogenic factor.[18]

Philadelphia, The Blakiston Company, 1951, pp. 264-272. (*f*) Berman, L.: Endocrine Treatment of Paget's Disease, Endocrinology **16**:109 (March-April) 1932; (*g*) Studies of Paget's Disease: II. The Effect of Adrenocortical Extract Treatment upon the Blood Phosphatase in Paget's Disease, ibid. **20**:226 (March) 1936.

30. Li and others.[22] Marx, W.; Simpson, M. E.; Li, C. H., and Evans, H. M.: Antagonism of Pituitary Adrenocorticotropic Hormone to Growth Hormone in Hypophysectomized Rats, Endocrinology **33**:102 (Aug.) 1943. Becks, H.; Simpson, M. E.; Marx, W.; Li, C. H., and Evans, H. M.: Antagonism of Pituitary Adrenocorticotropic Hormone (ACTH) to Action of Growth Hormone on Osseous System of Hypophysectomized Rats, ibid. **34**:311 (May) 1944.

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32. Apperly, F. L., and Cary, M. K.: A Note on Glucose Tolerance in Paget's Disease (Osteitis Deformans), Am. J. M. Sc. **192**:702 (Nov.) 1936.

33. Evans, H. M.; Meyer, K.; Simpson, M. E., and Reichert, F. L.: Disturbance of Carbohydrate Metabolism in Normal Dogs Injected with Hypophyseal Growth Hormone, Proc. Soc. Exper. Biol. & Med. **29**:857 (April) 1932. Young, F. G.: Permanent Experimental Diabetes Produced by Pituitary (Anterior Lobe) Injections, Lancet **2**:372 (Aug. 14) 1937; Experimental Investigations on the Relationship of the Anterior Hypophysis to Diabetes Mellitus, Proc. Roy. Soc. Med. **31**:1305 (Sept.) 1938. Campbell, J., and Best, C. H.: Production of Diabetes in Dogs by Anterior-Pituitary Extracts, Lancet **1**:1444 (June 25) 1938. Dohan, F. C., and Lukens, F. D. W.: Persistent Diabetes Following Injection of Anterior Pituitary Extract, Am. J. Physiol. **125**:188 (Jan.) 1939. Houssay, B. A., and Potick, D.: Antagonisme entre l'hypophyse et l' insuline chez le crapaud, Compt. rend. Soc. biol. **101**:940 (July 17) 1929. Richardson, K. C., and Young, F. G.: Histology of Diabetes Induced in Dogs by Injection of Anterior-Pituitary Extracts, Lancet **1**:1098 (May 14) 1938. Houssay, B. A.: Hypophysis and Metabolism, New England J. Med. **214**:961, and 971 (May 14) 1936. Price, W. H.; Cori, C. F., and Colowick, S. P.: Effect of Anterior Pituitary Extract and of Insulin on Hexokinase Reaction, J. Biol. Chem. **160**:633 (Oct.) 1945.

Moehlig and Abbott [31d,e] demonstrated a high incidence of impaired carbohydrate metabolism and familial diabetes, and also a tendency toward greater than normal height and obesity in their patients with Paget's disease. However, evidence has been presented that the incidence of impaired dextrose tolerance among patients with Paget's disease is no higher than that found among normal persons of the same age group.[34]

Gutman and Kasabach [13a] hold that Paget's disease is due to a local disturbance in bone metabolism. We are in accord with their viewpoint. Newer theories incorporate a second enzyme mechanism for endochondral calcification (phosphorylative glycogenolysis) with alkaline phosphatase in normal bone physiology.[35] On the basis of the foregoing, it might be conjectured that altered anterior pituitary function influences either or both of these enzyme mechanisms, causing the characteristic bone lesions of Paget's disease.

Since osteitis deformans occurs more frequently among persons of the older age groups, it is possible that along with evidence of diminished endocrine activity [36] there is an increase in pituitary growth hormone secretion which has a direct influence on osteoblastic activity and bone metabolism. Why this overproduction does not occur in all older persons is unknown. It has been shown that some older patients have a negative nitrogen balance [37] and decreased androgen levels which may stimulate the anterior pituitary gland to produce increased amounts of growth

34. Schneeberg, N. G.: Observations on the Glucose Tolerance Test in Paget's Disease (Osteitis Deformans), Am. J. M. Sc. **219**:664 (June) 1950. Deren, M. D.: Dextrose Tolerance in Aged, J. Lab. & Clin. Med. **22**:1138 (Aug.) 1937. Himsworth, H. P., and Kerr, R. B.: Age and Insulin Sensitivity, Clin. Sc. **4**:153 (Dec.) 1939. Hofstatter, L.; Sonnenberg, A., and Kountz, W. B.: Glucose Tolerance in Elderly Patients, Biol. Symposia **11**:87, 1945. Smith, L. E., and Shock, N. W.: Intravenous Glucose Tolerance Tests in Aged Males, J. Gerontol. **4**:27 (Jan.) 1949.

35. Gutman, A. B.: Current Theories of Bone Salt Formation with Special Reference to Enzyme Mechanisms in Endochondral Calcification, Bull. Hosp. Joint Dis. **12**:74 (Oct.) 1951. Howard, J. E.: Metabolism of Calcium and Phosphorus in Bone, Bull. New York Acad. Med. **27**:24 (Jan.) 1951.

36. (*a*) Thewlis, M. W.: The Care of the Aged (Geriatrics), Ed. 5, St. Louis, C. V. Mosby Company, 1946, p. 71. (*b*) Goldzieher, M. A.: Endocrine Aspects of Senescence, Geriatrics **1**:226 (May-June) 1946. (*c*) Benedict, F. G.: Old Age and Basal Metabolism, New England J. Med. **212**:1111 (June 13) 1935. (*d*) Boothby, W. M., and Sandiford, I.: Summary of Basal Metabolism Data on 8,614 Subjects with Special Reference to Normal Standards for Estimation of Basal Metabolic Rate, J. Biol. Chem. **54**:783 (Dec.) 1922. (*e*) Lewis, W. H., Jr.: Changes with Age in Basal Metabolic Rate in Adult Men, Am. J. Physiol. **121**:502 (Feb.) 1938. (*f*) Du Bois, E. F.: Lane Medical Lectures: Mechanism of Heat Loss and Temperature Regulation, Stanford Univ. Publ., Univ. Series, M. Sc. **3**:323, 1937. (*g*) Bruger, M., and Rosenkrantz, J. A.: Arteriosclerosis and Hypothyroidism: Observations on Their Possible Interrelationship, J. Clin. Endocrinol. **2**:176 (March) 1942. (*h*) Turner, H. H.: Endocrine Aspects of Gerontology, Geriatrics **4**:74 (March-April) 1949.

37. Albanese, A. A.; Higgons, R. A.; Vestal, B.; Stephanson, L., and Malsch, M.: Protein Requirements of Old Age, Geriatrics **7**:109 (March-April) 1952. MacCallum, W. G.: A Textbook of Pathology, Ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 65. Simms, H. S., and Stolman, A.: Changes in Human Tissue Electrolytes in Senescence, Science **86**:269 (Sept. 17) 1937.

hormone for nitrogen conservation.[38] Perhaps in others there are adequate androgenic hormones to prevent nitrogen loss [39]; hence this stimulus is lacking.

An objection to this hypothesis might be raised by some who point out that in acromegaly and gigantism associated with overproduction of growth hormone one does not find the characteristic bone lesions of Paget's disease. However, there is one distinct difference; patients with acromegaly or gigantism are usually in positive nitrogen balance. How this factor may influence the final picture is unknown.

Another important element is the role of alkaline phosphatase in the synthesis of fibrous protein, which is essential in normal bone physiology. As mentioned earlier, growth hormone causes a rise in bone and serum alkaline phosphatase.[25] However, there is insufficient knowledge concerning the effects of growth hormone on the synthesis of proteins.[14]

It is apparent, therefore, that although the above working hypothesis may be attractive there is still much to be learned about the actual cause of Paget's disease of bone.

AGE

Patients with Paget's disease are usually in the older age group, with most of the patients being between 40 and 60 years old.[40] However, the younger groups are not exempt, and a number of patients in the third decade have been observed.[41] Figure 1 summarizes the ages of our patients upon their admission to the hospital and also upon onset of the disease. In addition, the age when sarcomatous changes occur in Paget's disease lesions is compared with the age of 25 patients in this hospital having bone sarcoma arising *de novo*.[42] Eighty-one per cent of patients

38. Long.[14] Bartlett, P.D., and Gaebler, O. H.: Anterior Pituitary Growth Preparations: Relationship Between Nitrogen Storage and Other Criteria of Activity, Endocrinology **43**:329 (Nov.) 1948.

39. Turner.[36b] Kenyon, A. T.; Knowlton, K.; Sandiford, I.; Koch, F. C., and Lotwin, G.: Comparative Study of Metabolic Effects of Testosterone Propionate in Normal Men and Women and in Eunuchoidism, Endocrinology **26**:26 (Jan.) 1940. Kenyon, A. T.; Sandiford, I.; Bryan, A. H.; Knowlton, K., and Koch, F. C.: Effect of Testosterone Propionate on Nitrogen, Electrolyte, Water, and Energy Metabolism in Eunuchoidism, ibid. **23**:135 (Aug.) 1938. Kenyon, A. T.; Knowlton, K., and Sandiford, I.: Anabolic Effects of Androgens and Somatic Growth in Man, Ann. Int. Med. **20**:632 (April) 1944. Kochakian, C. D.: Protein Anabolic Effects of Steroid Hormones, Vitamins & Hormones **4**:255, 1946. Papanicolaou, G. N., and Falk, E. A.: General Muscular Hypertrophy Induced by Androgenic Hormone, Science **87**:238 (March 11) 1938. Simonson, E.; Kearns, W. M., and Enzer, N.: Effect of Oral Administration of Methyltestosterone on Fatigue in Eunuchoids and Castrates, Endocrinology **28**:506 (March) 1941. Kenyon, A. T.; Knowlton, K.; Lotwin, G., and Sandiford, I.: Metabolic Response of Aged Men to Testosterone Propionate, J. Clin. Endocrinol. **2**:690 (Dec.) 1942.

40. (*a*) Packard and others.[8e] (*b*) Dickson and others.[13b] (*c*) Kay, H. D.; Levy-Simpson, S.; Riddoch, G., and Vilvandre, G. E.: Osteitis Deformans with Roentgenographic Section, Arch. Int. Med. **53**:208 (Feb.) 1934. (*d*) Newman, F. W.: Paget's Disease: A Statistical Study of 82 Cases, J. Bone & Joint Surg. **28**:798 (Oct.) 1946. (*e*) Jaffe, H. L.: Paget's Disease of Bone, Arch. Path. **15**:83 (Jan.) 1933. (*f*) Goldenberg, R. R.: The Skeleton in Paget's Disease, Bull. Hosp. Joint Dis. **12**:229 (Oct.) 1951.

41. Paget.[5] Packard and others.[8e] Newman.[40d] Goldenberg.[40f] Wagner, M.: Report of Case of Paget's Disease in 18-Year Old Male, with Review of Literature, Wisconsin M. J. **46**: 1098 (Nov.) 1947.

42. The following types of bone neoplasms were included: osteogenic sarcoma in 11 patients, giant-cell tumor in 8, osteogenic chondrosarcoma in 2, reticulum-cell sarcoma in 2, liposarcoma in 1, and myxoliposarcoma in 1 patient.

with Paget's disease gave their ages as between 41 and 70 upon admission to the hospital. The average age of the entire group was 55 years. Sixty-four per cent were apprised of the diagnosis when they were between 31 and 50 years of age. The average age at onset of the disease was 41 years. Approximately 14% of the patients were aware of their disease between 21 and 30 years of age. The patients who had sarcomatous changes in their bone lesions were much older than the group of 25 patients who had primary bone neoplasms. Eighty per cent of the latter group were 10 to 40 years of age, in contrast to the patients with Paget's disease and

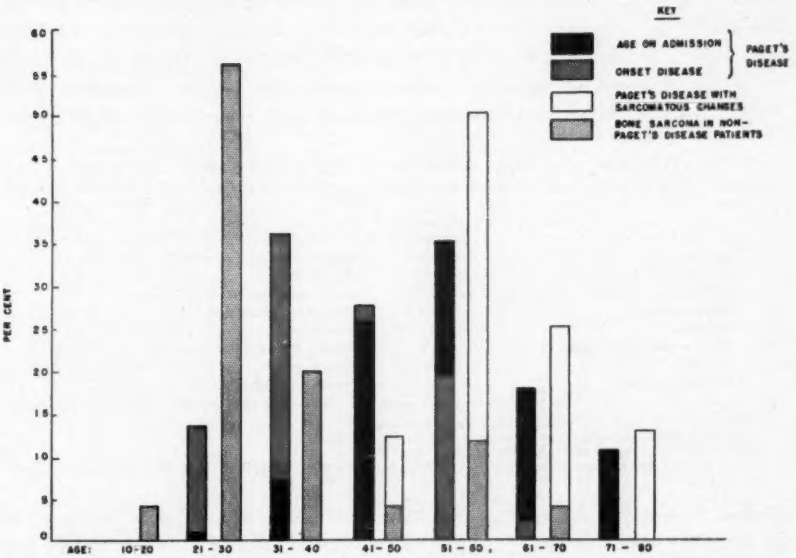

Fig. 1.—Age incidence among patients with Paget's disease of bone at time of admission and at time diagnosis was established; also age when sarcomatous changes take place in Paget's disease as compared with age of patients having bone sarcomata arising in normal bone.

sarcoma, who were all 41 to 80 years of age. These figures are in agreement with those of a previous series,[40f] in which 75% of patients with sarcoma in normal bone were between 10 and 25 years of age. Such statistics have also been reported for younger children, but in a Veterans Hospital they are not available.

SEX

This disorder occurs twice as often in males as in females,[43] though some observers indicate that the ratio of males to females may be 1 : 1.[44] Our present study does not present accurate sex ratio figures, since the population of this hospital is predominantly male.

43. Roberts and Cohen.[7b] Packard and others.[9e] Footnote 13.

44. Paget.[5] Newman.[40d]

RACE

Race was not a significant factor. Approximately 10% of the patients were Negro; the remainder were white. At this hospital the ratio of Negro to white patients admitted is usually about 1 : 10.

FAMILY HISTORY

Paget's disease may be found in families.[45] In this series seven patients had relatives with Paget's disease; two patients had two or more members of the family similarly afflicted. Our family history statistics might be unsatisfactory, since this was one of the elements for which many patients could not give accurate information. Table 1 details the family history as given by patients at the time of admission or in a subsequent questionnaire. One may note that families of patients with Paget's disease have hypertension, carcinoma, greater than normal height, heart

TABLE 1.—*Incidence of Disease in Families of Patients with Paget's Disease of Bone*

Disease	No. of Persons Affected	Disease	No. of Persons Affected
Hypertension	12 *	Rheumatoid arthritis	3
Carcinoma	11	Nephritis	2
Tallness (over 5 ft. 10 in.)	11 †	Arteriosclerosis	2
Heart disease	8	Coronary thrombosis	2
Diabetes	8 ‡	Sciatica	1
Paget's disease of bone	7 §	Benign tumor of stomach	1
Obesity	5	Tuberculosis	1
Cerebral accident	4	Nephrolithiasis	1

* Four patients had two relatives each with hypertension.
† Three patients each had two relatives who were abnormally tall.
‡ One patient had two relatives with diabetes.
§ One patient had three relatives, and one patient had two relatives with Paget's disease of bone.

disease, or diabetes oftener than they have osteitis deformans. Again, this may not be entirely correct because of the patient's lack of knowledge of family history and of correct diagnosis.

SYMPTOMS

Patients with osteitis deformans frequently have no symptoms referable to this disorder [46] and it may be found only incidental to other roentgenologic studies. When symptoms are a feature, bone pain is the predominant complaint (Table 2). There were 55 patients with the complaint of bone pain (in 28 in the lower extremities, hips, or pelvis; in 24 in the back and scapula; in 3 in the upper extremities). Other symptoms were defective hearing, visual disturbances, tinnitus, fatigue, headaches, urinary complaints and calculi, dyspnea, increasing head and hat size, gait disturbances, vertigo, angina pectoris, swelling and ulceration over affected bone parts, and reduction of stature in the later stages. This has been the experience of other workers.[47]

45. Roberts and Cohen.[7b] Footnote 13. Goldenberg.[40f] Rast, H., and Weber, F. P.: Paget's Bone Disease in 3 Sisters, Brit. M. J. **1**:918 (May 1) 1937.

46. Gutman and Kasabach.[13a] Kay and others.[40c]

47. Footnote 13. Newman.[40d]

PAST HEALTH

A review of the previous medical history (Table 3) of these patients demonstrates that 17 were prone to pathological or nonpathological bone fractures. Nine patients had a past history of diabetes; 6 had renal lithiasis; 11 had gonorrhea, and 4, syphilis.

PHYSICAL FINDINGS

The physical findings (Table 4) are interesting and correlate with the symptoms reported by the patients. Neuromuscular disturbances head the list, with 45 patients having sensory, reflex, motor, gait, and central nervous system changes. Twenty-

TABLE 2.—*Incidence of Symptoms in Patients with Paget's Disease of Bone*

Symptom	Incidence	Symptom	Incidence
Bone pain	55	Vomiting	6
Back and scapula	24	Weight loss	5
Lower extremities, hips, and pelvis	28	Abdominal pains	5
Upper extremities	3	Bronchial asthma	4
Defective hearing	14	Rectal bleeding	4
Headaches	14	Ankle swelling	4
Urinary disturbance including calculi	14	Reduction in stature	3
Dyspnea	11	Diarrhea	3
Increase in hat size	10	Insomnia	3
Vertigo	8	Claudication	3
Cough	8	Kidney region pain	3
Gait disturbance	8	Hoarseness	2
Angina pectoris	7	Chest pain	1
Swelling and ulceration of lower extremity	7	Poor memory	1

TABLE 3.—*Past Health*

Disease or Operation	Incidence	Disease or Operation	Incidence
Fracture, pathological and nonpathological	17	Pneumonia	2
Gonorrhea	11	Gout	2
Diabetes	9	Hemorrhoidectomy	2
Nephrolithiasis	6	Jaundice	2
Syphilis	4	Coronary thrombosis	2
Duodenal ulcer	4	Cholera	1
Malaria	3	Rheumatic fever	1
Prostatectomy for hypertrophied prostate	3	Tuberculosis	1
Head injury	2	Bronchial asthma	1
Typhoid	2	Tumor of nose	1
		Tumor of mouth	1
		Frequent carbuncles	1

five patients had cardiac abnormalities; 23 were obese; 19 had prominence of the skull or jaw; 17 had bowing of the lower extremities; 17 had emphysema or increased anteroposterior chest diameter; 17 had hypertension; 10 patients were taller than normal (more than 5 ft. 10 in. [177.8 cm.] tall); 9 had deformity of the pelvis or hip, and 8 revealed a deformity of the clavicle.

Osteitis deformans is supposedly associated with elevation of the skin temperature over the affected bones.[48] To check the validity of this contention, we ascer-

48. (*a*) Snapper, I.: Medical Clinics on Bone Diseases: A Text and Atlas, New York, Interscience Publishers, Inc., 1943, p. 1942; Ed. 2, 1949, pp. 164-179. (*b*) Klippel, M., and Weil, P.: Maladie osseuses de Paget unilaterale avec hypertherme locale et nodosités d'Heberden du côté correspondant, Rev. neurol. **16**:2028, 1908.

tained the skin temperatures over various regions of the skeletal structure in four patients. The roentgenograms were reviewed and the affected bones recorded alongside the skin temperature findings (Table 5). Except in Patient M. S., whose skin temperatures were elevated over the affected skull parts, there was no correlation between skin temperature and bone involvement. Though this does not agree with

TABLE 4.—*Physical Findings*

Finding	Incidence	Finding	Incidence
Neuromuscular disorders	45	Edema of lower extremity	5
Cardiac abnormalities	25	Abnormal physical signs in chest	5
Overweight (weight, 180-310 lb.)	23	Peripheral arteriosclerosis	2
Prominent skull or jaw	19	Atrophic testes	2
Bowing of lower extremities	19	Enlarged testis	1
Emphysema or increased anteroposterior diameter of chest	17	Mass, anterior rectal wall	1
Hypertension	17	Mass, left shoulder	1
Enlarged prostate	15	Mass, right ilium	1
Tallness, over 5 ft. 10 in.	10	Mass, right hip	1
Hepatic enlargement	9	Mass, right lower abdominal quadrant	1
Deformity of pelvis or hip	9	Atrophy of right shoulder	1
Deformity of clavicle	8	Enlarged thyroid	1

TABLE 5.—*Correlation of Skin Temperature with Roentgenologic Evidence of Presence of Paget's Disease of Bone**

Patient	M. S.		J. P.		M. M.		P. G.	
	Elevated Skin Temperature	Roentgen Signs	Elevated Skin Temperature	Roentgen Signs	Elevated Skin Temperature	Roentgen Signs	Elevated Skin Temperature	Roentgen Signs
Skull								
Anterior								
Right	+	+	0	0	0	0	+	0
Left	+	+	0	0	+	0	+	0
Posterior								
Right	+	+	0	0	0	0	0	0
Left	+	+	0	0	0	0	0	0
Pelvis								
Posterior								
Right	0	0	0	0	0	+	0	0
Left	0	0	0	+	0	+	0	0
Long bones, femur								
Right	0	+	0	+	+	+	0	+
Left	0	+	0	+	0	+	0	0

* Plus sign indicates presence and minus sign absence of finding.

previous reports, it is possible that in the more acute stages skin temperature is elevated.

ASSOCIATED DIAGNOSES AND COMPLICATIONS

Table 6 records other diagnoses made in addition to the final diagnosis of Paget's disease. There were 38 patients who had an additional diagnosis of arthritis (rheumatoid, osteoarthritis, gouty, and mixed). Twenty-six had arteriosclerotic or hypertensive cardiovascular disease; 24 were obese; 20 had salivary calculi; 17 had pathological fractures; 15 had generalized arteriosclerosis, and 8 had sarcomatous changes. One patient had multiple myeloma in addition to Paget's disease.

From the foregoing, it is apparent that the arthritides may be coexistent with Paget's disease of bone. In addition, because of the age of these patients, hypertensive or arteriosclerotic cardiovascular disease is the expected finding rather than the

TABLE 6.—*Associated Diagnoses*

Diagnosis				Incidence
Arthritis, all types				38
Arteriosclerotic or hypertensive cardiovascular disease				26
Obesity				24
Salivary calculus				20
Pathological fractures				17
Hypertrophied prostate				16
Generalized arteriosclerosis				15
Duodenal or gastric ulcer				11
Diabetes				9
Hemorrhoids				9
Herniae, all types				9
Neuroses				8
Carcinoma				7
	Rectum	1	Testis	1
	Colon	1	Supraorbital area	1
	Lung	1	Bladder	1
	Unknown site	1		
Pulmonary fibrosis				4
Renal calcinosis or lithiasis				4
Cellulitis, lymphangitis, or thrombophlebitis				4
Syphilis, all stages				4
Cirrhosis of liver				4
Dermatitides				4
Arteriolar nephrosclerosis				3
Renal inflammatory disease				3
Colitis				3
Bronchitis				3
Pneumonia				3
Varicose ulcers				3
Diverticulosis of colon				2
Osteomyelitis				2
Optic atrophy and neuritis				2
Cholecystitis				1
Pulmonary edema				1
Duodenal diverticulum				1
Gynecomastia				1
Chronic pleuritis				1
Rheumatic heart disease				1
Epididymitis				1
Glaucoma				1
Trichinosis				1
Papilloma of bladder				1
Phimosis				1
Hydrocele				1
Bronchial asthma				1
Paraplegia				1
Multiple myeloma				1

unusual. However, Harrison and Lennox [49] found that 39% of their patients with Paget's disease had valvular calcification. They stated that this incidence was five times that in a control series of the same age. It is their opinion that in Paget's

49. Harrison, C. V., and Lennox, B.: Heart Block in Osteitis Deformans, Brit. Heart J. **10**:167 (July) 1948.

disease calcium metabolism is labile, and calcium is readily deposited on valves and in the conduction system, causing heart block. Furthermore, one of the well-known features of the pathology of osteitis deformans is the hyperemia and increased vascularity of bones. Many neurosurgeons operating on a Pagetoid skull have encountered difficulty with hemorrhage. Edholm and co-workers [50] demonstrated that this increased bone vascularity is like an arteriovenous aneurysm or arteriovenous shunt and was the cause of cardiac failure and high pulse pressure in their patients with Paget's disease.

Urinary calculi are not infrequently found in patients with Paget's disease.[51] They were also noted in the present series. Since blood calcium and inorganic phosphate levels are usually normal in this disorder, this complication is not easily explained. It has been speculated that hypercalciuria probably develops in some patients with osteitis deformans during one phase of the pathological changes in bone when calcium is more labile.[52] The importance of colloids in Paget's disease is not known, but in the light of recent studies dealing with the effect of colloids in renal lithiasis [53] it is possible that in Paget's disease of bone there is a deficiency of protective colloids.

The frequent finding of salivary calculi may or may not be of importance. Patients and normal persons of all ages may have salivary calculi. However, since alkaline phosphatase is a component of normal saliva, a rise of serum alkaline phosphatase might cause a similar rise in salivary phosphatase, with a resultant change in oral metabolism. This is an excellent field for further investigation by members of the dental profession.

Nine of our patients had frank diabetes mellitus. Since on most of our 111 patients merely single fasting blood glucose studies rather than true dextrose-tolerance studies were made, no attempt is made to draw any conclusions concerning the incidence of diabetes in this series.

One patient had coexistent multiple myeloma. Diagnosis was made by biopsy. There are only three published instances of coexistent multiple myeloma in Paget's disease.[54] Reich and Brodsky,[54a] who reported the first case, mentioned an unpublished case. The one patient in this series will be reported on separately (Dr. Frederick Bailey, Veterans Administration Hospital, Bronx, N. Y.). The three published cases and the two unreported cases make a total of five known cases.

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50. Edholm, O. G.; Howarth, S., and McMichael, J.: Heart Failure and Bone Blood Flow in Osteitis Deformans, Clin. Sc. **5**:249 (Dec.) 1945.

51. Dickson and others.[13b] Newman.[40d] Goldstein, A. E., and Abeshouse, B. S.: Urinary Calculi in Paget's Disease (Osteitis Deformans), Am. J. Surg. **30**:359 (Nov.) 1935.

52. (*a*) Harrison and Lennox.[40] (*b*) Reifenstein, E. C., Jr., and Albright, F.: Paget's Disease: Its Pathologic Physiology and Importance of This in Complications Arising from Fracture and Immobilization, New England J. Med. **231**:343 (Sept. 7) 1944.

53. Butt, A. J., and Hauser, E. A.: The Importance of Protective Urinary Colloids in the Prevention and Treatment of Kidney Stones, Science **115**:308 (March 21) 1952.

54. (*a*) Reich, C., and Brodsky, A. E.: Coexisting Multiple Myeloma and Paget's Disease of Bone Treated with Stilbamidine, J. Bone & Joint Surg. **30A**:642 (July) 1948. (*b*) Hanisch, C. M.: Paget's Disease Complicated by Multiple Myeloma, Bull. Hosp. Joint Dis. **11**:43 (April) 1950.

Patients with Paget's disease may demonstrate neurological and/or psychiatric symptoms. In some patients these are secondary to bone changes of the skull and vertebrae, while in others there may be lesions of the spinal cord attributable to the disease per se.[55] Wycis [56] felt that basilar impression (platybasia) had some relation to the neurological complications. Other clinical reviews reported neuralgia, deafness, muscular weakness, reflex changes, speech difficulty, visual disturbances, and

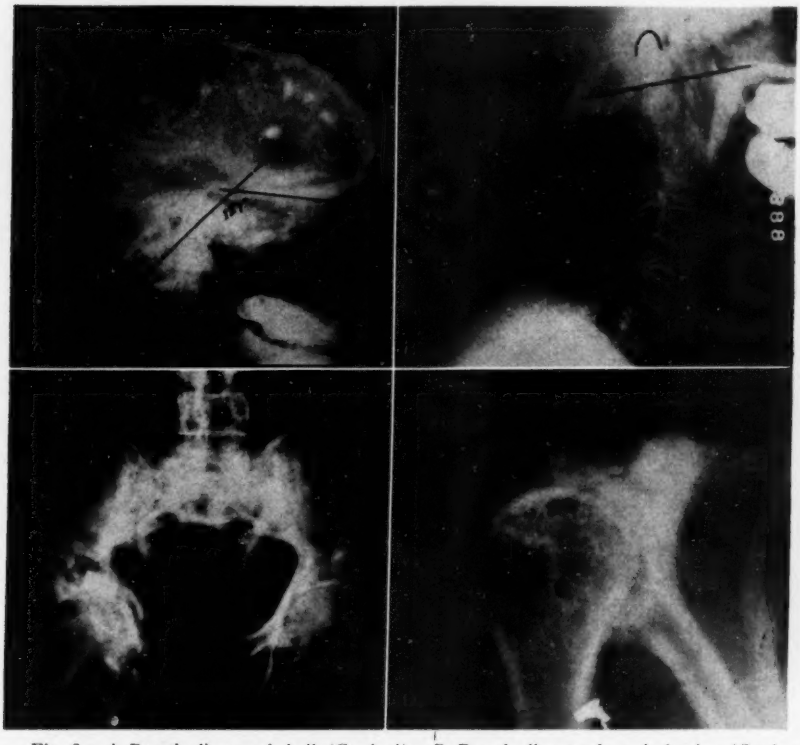

Fig. 2.—*A*, Paget's disease of skull (Grade 4). *B*, Paget's disease of cervical spine (Grade 2). Chamberlain's line and tip of odontoid process are outlined. *C*, Paget's disease of pelvis (Grade 4). *D*, Paget's disease of scapula (Grade 4) and of humerus (Grade 3).

55. (*a*) Gross, R. J., and Yelin, G.: Multiple Myeloma Complicating Paget's Disease, Am. J. Roentgenol. **65**:585 (April) 1951. (*b*) Wyllie, W. G.: Occurrence in Osteitis Deformans of Lesions of Central Nervous System: Report of 4 Cases, Brain **46**:336 (Oct.) 1923. (*c*) Rabiner, A. M., and Hand, M. H.: Paget's Disease and Central Nervous System, New York J. Med. **47**:2689 (Dec. 15) 1947. (*d*) Lévi, L.: Un cas d'ostéite déformante de Paget: Interprétation des lésions de la moelle épinière, abstracted, Compt. rend. Soc. biol. **4**:272, 1897.

56. Wycis, H. T.: Basilar Impression (Platybasia): A Case Secondary to Advanced Paget's Disease with Severe Neurological Manifestations; Successful Surgical Result, J. Neurosurg. **1**:299 (Sept.) 1944.

abnormal ocular signs in Paget's disease.[57] Many of these symptoms are due to the effect of bony deformities of the skull and spine on cranial nerves. Rabiner and Hand [55c] maintain that torsion, stretching, and sagging of the brain stem, as a result of bony deformities, are responsible for cranial nerve and pyramidal tract signs. Langsteiner [58] and Miner [59] have reported trigeminal neuralgia in Paget's disease. It was pointed out above that 45 patients in this series had neuromuscular disturbances. In some, platybasia, or basilar impression of the skull, may be the causative factor. Figure 2 illustrates skull changes in a patient with advanced Paget's disease.

With reference to sarcomatous changes in Paget's disease, it might be reiterated that Paget [6b] noted sarcomatous changes in his early cases. Ochsner and Gage [60] reviewed 31 cases, and Miner [59] referred to 65 patients, with sarcoma in osteitis deformans. The incidence of sarcoma in Paget's disease is given as between 5 and 14%.[61] Eight patients, or 7.2%, in our series had sarcoma. Speiser [61e] remarked that sarcoma of bone occurred 30 times as often among patients with Paget's disease as it did among the general population of a similar age group. One cannot underestimate the importance of frequently repeated skeletal roentgenologic studies in patients with known Paget's disease.[61] Why osteitis deformans provokes sarcomatous changes is unknown. It is possible that the rapid proliferation of young cells is an influencing factor.[62] In passing it should be mentioned that the neoplastic change is not always osteogenic sarcoma; occasionally one finds chondrosarcoma,[63] giant-cell tumor,[40f] and fibrosarcoma.[64] There may also be simultaneous sarcomatous changes occurring in several bones.[48a]

57. Fournier.[11b] Kay and others.[40c] Fowler, E. P. Jr.: Symposium: Neural Mechanism of Hearing; Etiological and Clinical Types of So-Called "Nerve Deafness" of Known Pathology or Etiology, Nerve Deafness from Non-Inflammatory Lesions, Laryngoscope **47**:586 (Aug.) 1937. Lindsay, J. R., and Perlman, H. B.: Paget's Disease and Deafness, Arch. Otolaryng. **23**:580 (May) 1936. Warren, S., and Agar, D. F.: Paget's Disease of Skull with Osteogenic Sarcoma, J. Missouri M. A. **45**:348 (May) 1948.

58. Langsteiner, F.: Trigeminusneuralgie bei Ostitis deformans (Paget) des Schädels, Klin. Wchnschr. **16**:503 (April 3) 1937.

59. Miner, I. E.: Sarcoma in Paget's Disease of Bone, Bull. Hosp. Joint Dis. **11**:26 (April) 1950.

60. Ochsner, A., and Gage, I. M.: Osteogenic Sarcoma Developing in Osteitis Deformans, S. Clin. North America **10**:851, 1930.

61. (*a*) Footnote 8*c*, *e* and *f*. (*b*) Miner.[59] (*c*) Kirshbaum, J. D.: Fibrosarcoma of Skull in Paget's Disease, Arch. Path. **36**:74 (July) 1943. (*d*) Gruner, O. C.; Scrimger, F. A. C., and Foster, L. S.: A Clinical and Histologic Study of a Case of Paget's Disease of the Bones with Multiple Sarcoma Formation, Arch. Int. Med. **8**:641 (June) 1912. (*e*) Speiser, F.: Sarkomatöse Entartung bei der Ostitis deformans, Arch. klin. Chir. **149**:274, 1928. (*f*) Stöhr, F.: Über Sarkombildung bei Ostitis deformans Paget, Wien. med. Wchnschr. **79**:1231 (Sept. 21) 1929.

62. Jaffe.[40e] Kirshbaum.[61c] Stöhr.[61f]

63. Grizaud, H.: Ostéite fibreuse deformante de Paget: ostéosarcoma et traumatisme, Presse méd. **44**:1018 (June 20) 1936.

64. Layani, F., and Olivier, C.: Ostéosarcome et maladie de Paget, Presse méd. **54**:145 (March 9) 1946.

BIOCHEMICAL STUDIES

Biochemical analyses are of great importance in the study of Paget's disease of bone. Serum calcium and inorganic phosphates are within the normal range.[65] Serum alkaline phosphatase is usually elevated,[66] while serum acid phosphatase[67] is usually normal except in rare cases with markedly elevated alkaline phosphatase, in which there may be some overlap, and an increase in acid phosphatase.

In this study serum calcium[68] was determined in 61 patients, with an average value of 10.5 mg. per 100 cc. (range, 8.7 to 12.7 mg. per 100 cc.). On 57 inorganic phosphate analyses[69] the average was 3.8 mg. per 100 cc. (range, 2.5 to 5.5 mg. per 100 cc.).

From 1941 through 1950 the alkaline phosphatase technique was altered three times at this hospital. The King-Armstrong method,[70] with normal values up to 13 units, was employed in 1941 through 1945. Twenty-four of our patients had alkaline phosphatase determinations by this method, six of whom had normal values. The average was 31.3 units (range, 5.5 to 103.7 units). Between 1946 and 1948 inclusive, the Bodansky procedure[71] with normal values up to 9 units was employed. Nineteen of our series were studied by this technique, and for 11 of these values were

65. O'Reilly and Race.[8j] Gutman and Kasabach.[13a] Footnote 40*c*, *d*, and *f*. Hunter, D.: Critical Review: The Metabolism of Calcium and Phosphorus and the Parathyroids in Health and Disease, Quart. J. Med. **24**:393 (April) 1931. Jerome, J. T., and Compere, E. L.: The Pathological and Biochemical Changes in Paget's Disease, Illinois M. J. **64**:449 (Nov.) 1933. Albright, F.; Aub, J. C., and Bauer, W.: Hyperparathyroidism: A Common and Polymorphic Condition as Illustrated by Seventeen Proved Cases from One Clinic, J. A. M. A. **102**:1276 (April 21) 1934.

66. (*a*) Gutman and Kasabach.[13a] (*b*) Newman.[40d] (*c*) Kay, H. D.: Plasma Phosphatase in Osteitis Deformans and in Other Diseases of Bone, Brit. J. Exper. Path. **10**:253 (Aug.) 1929; (*d*) Phosphatase in Growth and Disease of Bone, Physiol. Rev. **12**:384 (July) 1932. (*e*) Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90 (April) 1930. (*f*) Gutman, A. B.; Gutman, E. B., and Kasabach, H.: Serum Phosphatase Activity in 17 Cases of Osteoporosis Circumscripta of the Skull, Proc. Soc. Exper. Biol. & Med. **33**:295 (Nov.) 1935. (*g*) Gutman, A. B., and Gutman, E. B.: Paget's Disease: Relative Constancy of Serum Phosphatase Levels over Periods up to 2 Years, ibid. **33**:150 (Oct.) 1935. (*h*) Gutman, A. B.; Tyson, T. L., and Gutman, E. B.: Serum Calcium, Inorganic Phosphorus, and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma, and Neoplastic Disease of the Bones, Arch. Int. Med. **57**:379 (Feb.) 1936. (*i*) Gutman, E. B.; Sproul, E. E., and Gutman, A. B.: Significance of Increased Phosphatase Activity of Bone at Site of Osteoplastic Metastases Secondary to Carcinoma of the Prostate Gland, Am. J. Cancer **28**:485 (Nov.) 1936.

67. Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase Activity of Serum of Normal Human Subjects, Proc. Soc. Exper. Biol. & Med. **38**:470 (May) 1938; "Acid" Phosphatase Occurring in Serum of Patients with Metastasizing Carcinoma of Prostate Gland, J. Clin. Invest. **17**:473 (July) 1938. Gutman, A. B.; Gutman, E. B., and Robinson, J. N.: Determination of Serum "Acid" Phosphatase Activity in Differentiating Skeletal Metastases Secondary to Prostatic Carcinoma from Paget's Disease of Bone, Am. J. Cancer **38**:103 (Jan.) 1940.

68. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461 (March) 1924.

69. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375 (Dec.) 1925.

70. King, E. J., and Armstrong, A. R.: Convenient Method for Determining Serum and Bile Phosphatase Activity, Canad. M. A. J. **31**:376 (Oct.) 1934.

71. Bodansky, A.: Phosphatase Studies: Determination of Serum Phosphatase; Factors Influencing Accuracy of Determination, J. Biol. Chem. **101**:93 (June) 1943.

found to be within normal limits. The average was 11.8 units (range, 1.5 to 44.0 units). Since 1949, all serum alkaline phosphatase levels have been determined by the technique of Shinowara and associates,[72] with normal values up to 8.6 units. Thirty-one patients had serum alkaline phosphatase analyses by this procedure. Six patients had normal levels. The average was 21.1 units (range, 3.3 to 91.4 units). One of the patients studied by this procedure returned subsequently for repeated studies. His highest alkaline phosphatase level was 126.0 units.

When the degree of roentgenologic bone involvement is classified as Grades 1 to 4 and correlated with the serum alkaline phosphatase level (Fig. 3), one notes that with advancement of bone involvement there is a rise in the serum alkaline phosphatase. It should be pointed out that 23 of the 74 patients who had both serum alkaline phosphatase analyses and roentgenologic studies had normal levels; 13 of those with normal values were among the patients with lower Grade 1 or 2 lesions.

Acid phosphatase was studied in 54 patients, with an average of 1.6 units (range, 0.0 to 7.9 units). There were five patients in this group who had elevation of acid phosphatase; three of these had Grade 4 roentgenographic changes, while two had Grade 2 bone involvement. Each of these five patients had alkaline phosphatase levels in the higher concentrations (69.6, 58.1, 89.2, 61.3, and 74.6 units). In the absence of metastatic carcinoma of the prostate, these patients probably had elevation of acid phosphatase because of overlap between the alkaline and the acid phosphatase zones.

Serum alkaline phosphatase determinations were made for five of the eight patients with sarcomatous changes in Paget's disease lesions. Values for two were normal, for two, slightly elevated, and for one, markedly elevated. Three of these eight patients had acid phosphatase analyses; all values were recorded as normal.

In the 25 patients with sarcoma arising in normal bone, referred to above, 16 alkaline phosphatase and 12 acid phosphatase studies were performed, and all results were normal; 7 of these patients had blood calcium and inorganic phosphate determinations which were normal. The finding of normal serum alkaline phosphatase is explained by reports of normal alkaline phosphatase in sarcomata with destructive lesions,[73] whereas there is marked elevation of alkaline phosphatase when the sarcomatous tissue consists of malignant osteoblasts.[74]

Other studies that were carried out are listed below:

1. The Schoenheimer-Sperry technique,[75] with normal values of 150 to 250 mg. per 100 cc., was employed to determine the serum cholesterol. There were 17 analyses, with an average level of 223 mg. per 100 cc. (range, 140 to 340 mg. per 100 cc.). Only five patients of this group had levels of more than 250 mg. per 100 cc.

72. Shinowara, G. Y.; Jones, L. M., and Reinhar, H. L.: The Estimation of Serum Inorganic Phosphate and "Acid" and "Alkaline" Phosphatase Activity, J. Biol. Chem. **142**:921 (Feb.) 1942.

73. Gutman and others.[60b] Bodansky, A., and Jaffe, H. L.: "Phosphatase Studies": III. Serum Phosphatase in Diseases of Bone; Interpretation and Significance, Arch. Int. Med. **54**: 88 (July) 1934.

74. Franseen, C. C., and McLean, R.: The Phosphatase Activity of Tissues and Plasma in Tumors of Bone, Am. J. Cancer **24**:299 (June) 1935. Woodward, H. Q., and Higinbotham, N. L.: The Correlation Between Serum Phosphatase and Roentgenographic Type Bone Disease, ibid. **31**:221 (Oct.) 1937.

75. Schoenheimer, R., and Sperry, W. M.: Micromethod for Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745 (Sept.) 1934.

2. Total serum protein and albumin and globulin concentrations were determined by the Weichselbaum [76] method, for which the normal values are 6 to 8% total serum protein, 4.5 to 5.5% albumin, and 1.5 to 3.0% globulin. There were 32 patients who had such studies, with an average total serum protein of 6.6% (range, 4.8 to 8.0%), an average albumin of 4.2% (range, 2.8 to 5.5%), and an average globulin of 2.4% (range, 1.2 to 3.7%). It is apparent that the proteins and fractions are normal in patients with Paget's disease.

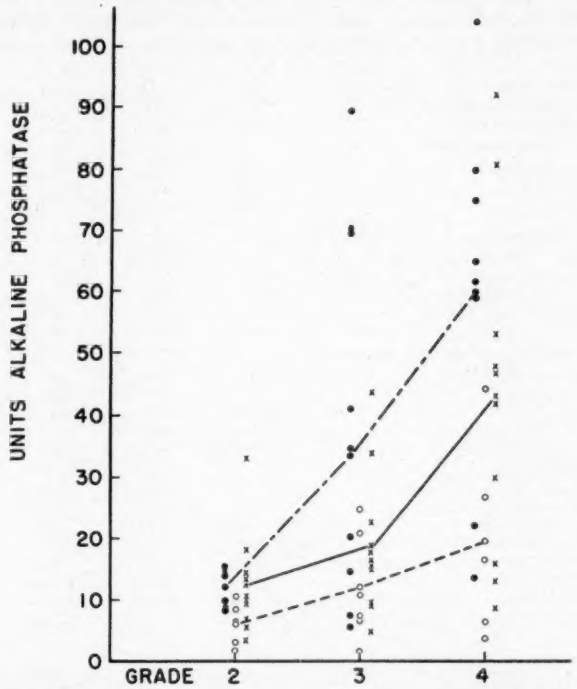

Fig. 3.—Serum alkaline phosphatase levels correlated with roentgenographic grade of bone involvement in 74 patients with Paget's disease of bone. King-Armstrong technique (results indicated by black dot) was used for 24 patients, 1941 to 1945. Bodansky technique (results indicated by circle) was used for 19 patients, 1946 to 1948. Technique of Shinowara and others (results indicated by ×) was used for 31 patients, 1949 to 1951.

3. The 24-hour urine specimens in eight patients were analyzed for 17-ketosteroids by the method of Drekter and co-workers [77] (normal values, 8 to 20 mg. in males). While levels in two of these patients were found to be definitely below normal, no definite conclusions may be drawn from this small series.

76. Weichselbaum, T. E.: Accurate and Rapid Method for Determination of Proteins in Small Amounts of Blood Serum and Plasma, Am. J. Clin. Path. (Tech. Sect.) **10**:40 (March) 1946.

77. Drekter, I. J.; Pearson, S.; Bartczak, E., and McGavack, T. H.: Rapid Method for Determination of Total Urinary 17-Ketosteroids, J. Clin. Endocrinol. **7**:795 (Dec.) 1947.

4. Basal metabolic rates were determined in 11 patients by the Roth and Roth technique.[78] With the use of ±15% as normal, only one had an elevation in basal heat production.

5. In five patients, the hemagglutination test of Heller and colleagues[79] for rheumatoid arthritis was performed, and in each the results were negative.

6. Antistreptolysin titer determinations in two patients gave normal results.

7. Bone marrow studies performed in four patients gave normal results.

TABLE 7.—*Results of Biochemical Studies on Four Patients with Paget's Disease of Bone*

Patient	M. S.	J. P.	M. M.	P. G.
Serum calcium, mg./100 cc.	10.6	10.7	10.8	10.9
Serum inorganic phosphate, mg./100 cc.	4.3	3.6	3.6	4.2
Serum alkaline phosphatase, units	126.0	10.6	27.5	10.5
Serum acid phosphatase, units	1.0	0.3	0.1	0.4
Total serum protein, %	7.2	6.1	6.0	6.7
Albumin	6.0	4.5	4.4	5.0
Globulin	1.2	1.6	1.6	1.7
Dextrose tolerance, true dextrose, mg./100 cc.				
Fasting	84	115	85	80
½ hr.	194	207	140	156
1 hr.	230	272	125	141
2 hr.	201	276	105	121
3 hr.	144	312	103	91
Insulin tolerance, true dextrose, mg./100 cc.				
Fasting	58	110	100	63
½ hr.	85	210	63	46
1 hr.	89	220	71	71
1½ hr.	97	124	67	71
2 hr.	89	140	58	54
Basal metabolic rate, %	+8	+16	+2	+12
17-ketosteroids, mg./24-hour urine	11.5	18.3	14.3	13.5
Rheumatoid arthritis agglutination	Neg.	Neg.	Neg.	Neg.
Red blood cells, million/cu. mm.	4.46	4.7	4.4	4.5
Hemoglobin, gm./100 cc.	14.2	15.9	14.7	15.5
Erythrocyte sedimentation rate, mm./hr.	21	22	18	8
Bone marrow	Normal	Normal	Normal	Normal
Urinalysis, routine	Normal	Normal	Normal	Normal

Table 7 summarizes a variety of laboratory studies in four typical patients to emphasize some of the points mentioned above. Two of these patients had diabetic dextrose-tolerance curves. None of these four patients was anemic, and each of them had normal bone marrow studies.

ROENTGENOLOGIC STUDIES

The patients included in this series demonstrated typical changes of Paget's disease roentgenographically. Table 8 outlines the frequency with which bones were involved in 95 patients with adequate roentgenograms. The pelvic bones were most frequently affected, followed by the skull, femur, lumbar spine, thoracic spine, tibia,

78. Roth, P., and Roth, H. P.: Metabolism: Apparatus and Methods, in Medical Physics, edited by O. Glasser, Chicago, The Year Book Publishers, Inc., 1944, Vol. I, pp. 718-724.

79. Heller, G.; Jacobson, A. S.; Kolodny, M. H., and Schuman, R. L.: Hemagglutination Test for Rheumatoid Arthritis: I. An Immunological Analysis of the Factors Involved in the Reaction, J. Immunol. **69**:627, 1952.

humerus, cervical spine, scapula, clavicle, sacrum (without other pelvic involvement), ribs, fibula, and mandible. This has been the experience of other investigators.[47] Most of the reported studies on Paget's disease emphasize bones other than the maxilla and mandible. However, Stafne and Austin [80] investigated 138 patients with Paget's disease and found involvement of 20 maxillae and 3 mandibles. In our series only one patient had osteitis deformans of the mandible. This figure might have been higher if we had directed our attention to facial bone pathology.

Pathological fractures are fairly common in Paget's disease,[81] and these usually heal with callus formation.[82] In our series there were 17 patients with roentgen evidence of pathological fracture through Paget's disease of bone.

TABLE 8.—*Roentgenologic Studies: Bones Affected*

Pelvis	60
Skull	40
Femur	
Right	39
Left	32
Lumbar spine	37
Thoracic spine	19
Tibia	
Right	9
Left	10
Humerus	
Right	9
Left	8
Cervical spine	6
Scapula	
Right	3
Left	5
Clavicle	
Right	3
Left	5
Ribs	4
Sacrum (other pelvic parts unaffected)	4
Fibula	
Right	3
Left	3
Mandible	1

In the present study the degree of bone involvement was graded 1 to 4. For correlation purposes, when the patient had multiple bone involvement, the bone showing the greatest degree was used as the basis of classification. In Grade 1, the finding was that of osteoporosis circumscripta of the skull with no other manifesta-

80. Stafne, E. C., and Austin, L. T.: A Study of Dental Roentgenograms in Cases of Paget's Disease (Osteitis Deformans), Osteitis Fibrosa Cystica, and Osteoma, J. Am. Dent. A. **25**:1202 (Aug.) 1938.

81. (*a*) Newman.[40d] (*b*) Goldenberg.[40f] (*c*) Traver, C. A.: Association of Fractures and Paget's Disease (Osteitis Deformans), New York J. Med. **36**:242 (Feb. 15) 1936. (*d*) Allen, M. L., and John, R. L.: Osteitis Deformans (Paget's Disease): Fissure Fractures, Their Etiology and Clinical Significance, Am. J. Roentgenol. **38**:109 (July) 1937. (*e*) Ghormley, R. K.; Sutherland, C. G., and Pollock, G. A.: Pathological Fractures, J. A. M. A. **109**:2111 (Dec. 25) 1937. (*f*) Rogers, M. H., and Ulin, R.: Fractures in Paget's Disease, J. Bone & Joint Surg. **18**:914 (Oct.) 1936.

82. Footnote 13. Jaffe.[40e] Goldenberg.[40f] Allen and John.[81d]

tions of Paget's disease in the remaining skeletal structures. In Grades 2, 3, and 4, there was definite structural enlargement of the bone, with associated thickening of the cortex and prominence of the bony trabeculations. The classification of Grades 2, 3, and 4 is purely an arbitrary one, with Grade 4 demonstrating the most advanced roentgenographic changes of Paget's disease, and Grades 2 and 3 the varying degrees of less advanced roentgenographic involvement. An example of Grade 4 involvement is presented in Figure 2, which illustrates involvement of the skull, pelvis, humerus, and scapula, and, although these bones had various degrees of involvement, the classification was Grade 4 because of the skull and pelvic findings.

It also seemed pertinent to determine whether sarcomatous changes occurred more readily in those bones which showed a greater degree of involvement. Of five patients whose roentgenograms were at hand, three patients had Grade 4 lesions, one Grade 3, and one Grade 2.

PATHOLOGY

Much has been written on the pathological physiology of osteitis deformans. A clear and concise description is found in the paper by Reifenstein and Albright.[52b] They point out that initially the lesion is a local one and causes destruction without regard to structure. This destruction makes the affected bone more susceptible to stresses and strains; hence the osteoblasts are stimulated to manufacture matrix, and with this stimulus alkaline phosphatase is increased. When the stresses and strains are constant, bone formation goes on simultaneously with destruction. However, when stresses and strains are of less magnitude, bone repair falls behind bone destruction. The destruction is not related to the mechanical requirements of the skeleton and, accordingly, results in a bone of poor architectural value.

It is not within the scope of this paper to review the field of pathology in Paget's disease. Figure 4 represents microscopic sections through a Paget lesion of bone in which sarcomatous changes have taken place. It will be noted that the typical irregular mosaic pattern of Paget's disease is present and is associated with a loose fibrosis of the interosseous spaces. These areas of simultaneous bone resorption and new bone deposition merge with the infiltrating osteogenic sarcoma. The latter consists principally of a highly cellular component with little bone matrix formation. The cells are spindle-shaped and are generally arranged in faint, large, irregular, whorled patterns. The cells, particularly the nuclei, vary considerably in size and shape. The nuclei also contain large nucleoli. Multinucleated tumor giant cells are frequent. The tumor is often associated with small irregular fragments of osteoid tissue. In some places this tissue appears to be invaded by the tumor, but in others it seems likely that osteoid is formed and growing with the neoplastic spindle cells. The other, less striking portions of the tumor are far less cellular and present a distinct bony and osteoid matrix. Here the cells, although much less numerous, also show considerable variation in size and shape, as well as many bizarre forms.

TREATMENT

The treatment of patients with Paget's disease of bone remains a challenge. Through the years treatment has been either symptomatic or general, but no specific therapy has been discovered. Calcium, high-vitamin diets, dihydrotachysterol,[83]

83. Coryn, G.: Les phosphatases du sang dans le diagnostic des affections osseuses, J. belge chir. **33**:213 (May) 1934.

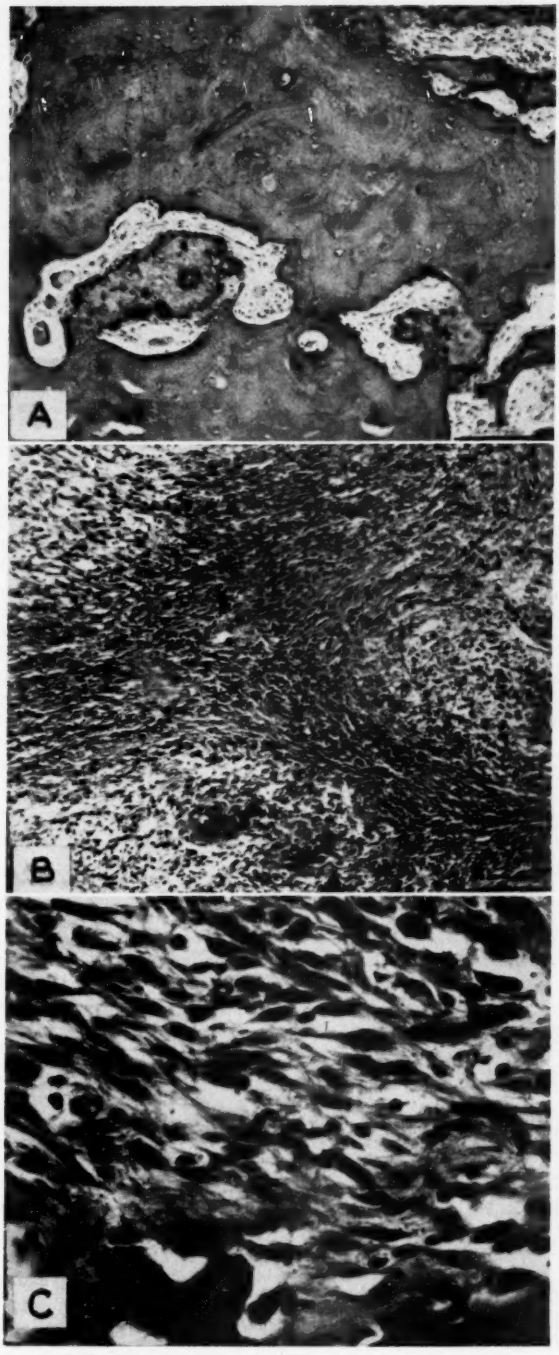

Fig. 4.—Paget's disease of bone with ostenogenic sarcoma. Hematoxylin and eosin stain. *A*, Paget's disease of bone; × 100. Characteristic mosaic pattern formed by irregular cement lines and scalloped edges of bone. *B*, low-power view of sarcomatous area; × 100. Note irregular fragments of osteoid. *C*, higher-power view of sarcomatous area; × 475. Spindle-shaped cells with many bizarre forms. Note osteoid at bottom of field.

potassium iodide,[84] Staphylococcus vaccine, arsenic, insulin,[84b] and irradiation [40f] have been prescribed without influence on the bone lesions. Pteroyltriglutamic acid (teropterin®),[40f] parathormone,[85] and aluminum acetate [86] have been administered with relief of bone pain but without effect on the pathological process. Berman [29f] believed that Paget's disease of bone was due to a relative deficiency of adrenal cortical hormones, with resultant imbalance of the parathyroid glands. He administered [29f,g] adrenal cortex extract. His patients not only showed marked clinical improvement but over a two-year period had a progressive decrease in serum alkaline phosphatase. Kay and associates [40c] also reported relief of bone pain following the administration of 0.3 gm. of adrenal extract three times a day.

TABLE 9.—*Change in Serum Alkaline Phosphatase, in Units, in Four Patients with Paget's Disease Following Oral Administration of Fifteen Milligrams of Folic Acid Daily for Four Weeks*

Patient	Initial	1 Wk.	2 Wk.	3 Wk.	4 Wk.	After Therapy
M. S.	126.0	116.0	123.0	120.0	115.0	128.0
J. P.	10.1	14.1	12.8	13.6	12.8	12.7
M. M.*	27.5	33.0	30.0	32.4	31.0	32.4
P. G.	10.5	9.8	10.1	8.5	9.3	9.8

* This patient was given folic acid for six months with a gradual rise in his serum alkaline phosphatase to 45.7 units without clinical improvement.

TABLE 10.—*Effect of Daily Intravenous Administration of Twenty Milligrams of Corticotropin on Serum Alkaline Phosphatase, in Units, of Two Patients with Paget's Disease*

	Patient	
Day	M. M.	M. S.
— 2	45.7	95.6
0	46.7	94.6
2	12.8	55.3
4	33.3	125.0
6	34.5	120.0
8	32.0	118.0
10	39.4 *	123.5
12	45.8	100.9 †
14	40.8	105.0
21	40.3	108.0

* Treatment was stopped on eighth day because signs of congestive failure developed.
† Treatment was stopped because of glycosuria, which cleared within four days following the discontinuance of therapy.

Recent experiments on the effect of folic acid on the alkaline phosphatase of chicken oviduct [87] suggested a study of the effect of folic acid on serum alkaline

84. (*a*) Paget.[5] (*b*) Moehlig, R. C., and Murphy, J. M.: Paget's Disease (Osteitis Deformans) with Reference to Role of Pituitary, Endocrinology **19**:515 (Sept.-Oct.) 1935.

85. Snapper.[48a] Van de Maele, M.: Contribution au traitement de la maladie de Paget, J. belge radiol. **25**:255, 1936.

86. Ghormley, R. K., and Hinchley, J. J.: Use of Aluminum Acetate in Treatment of Malacic Diseases of Bone, J. Bone & Joint Surg. **26**:811 (Oct.) 1944. Helfet, A. J.: New Conception of Parathyroid Function and Its Clinical Application: Preliminary Report on Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminum Acetate, Brit. J. Surg. **27**:651 (April) 1940.

87. Andrus, M., and Zarrow, M. X.: Amount of Alkaline Phosphatase in the Oviduct of Folic Acid Deficient Chicks, Proc. Soc. Exp. Biol. & Med. **72**:714 (Dec.) 1949.

phosphatase in Paget's disease. Additional studies included the effects of corticotropin (ACTH).

Table 9 details the changes in serum alkaline phosphatase levels following the daily administration of 15 mg. of folic acid to four patients for four weeks. During this period alkaline phosphatase levels vacillated, and at the end of this period no conclusions could be drawn because the changes observed were too slight. Patient M. M. was maintained with folic acid therapy for six months. At the end of four weeks there was a rise in alkaline phosphatase by 6.5 units, and after six months there was a rise of 18.2 units as compared with the initial level.

The effect of daily intravenous administration of 20 mg. of corticotropin on serum alkaline phosphatase in two patients is summarized in Table 10. In Patient M. S. there was a prompt fall in serum alkaline phosphatase within 48 hours, but two days later the alkaline phosphatase rose to levels higher than the initial level and remained elevated after the discontinuance of therapy. Patient M. M. had a fall in serum alkaline phosphatase in a similar period, but the rebound was not as marked, and the levels after discontinuance of therapy were slightly lower than the baseline determination. Therefore, although corticotropin will cause a fall in serum alkaline phosphatase, it is not maintained. Clinically, as reported by previous investigators who administered a variety of medications, corticotropin causes subjective improvement, with relief of bone pain and increase in general well-being but without demonstrable effect on the bone lesions. Because of the high incidence of cardiac disease in patients with Paget's disease, corticotropin or cortisone is utilized with possible danger of plunging the patient into congestive failure, as in Patient M. M.

SUMMARY

The clinical records of 111 patients are analyzed and summarized. In eight of these patients sarcomatous changes developed, and one patient had multiple myeloma.

Folic acid and corticotropin were administered to four and two patients, respectively, and their effects on serum alkaline phosphatase are recorded.

The literature on various aspects of Paget's disease of bone is reviewed.

Veterans Administration Hospital, East Orange, N. J. (Dr. Rosenkrantz).

Dr. H. L. Jaffe, of the Hospital for Joint Diseases, New York, gave constructive criticism. Dr. Benjamin Gordon, Dr. Theodore Ehrenreich, and Dr. Bernard Klein, of the Laboratory Services of the Bronx Veterans Administration Hospital, assisted with the pathological and biochemical material. Mr. Sidney Shapiro, Mr. Masayuki M. Nakamura, Mr. George Davis, and Mr. Paul Newman, of the Medical Illustration Service of this hospital, prepared the illustrations. Miss Margaret Kinney and members of the medical library staff assisted in preparation of the references.

HEMOPERICARDIUM COMPLICATING MYOCARDIAL INFARCTION IN THE ABSENCE OF CARDIAC RUPTURE

Report of Three Cases

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IT HAS been established recently by Goldstein and Wolff [1] that in patients with acute myocardial infarction anticoagulant therapy with bishydroxycoumarin (dicumarol®) may be followed by hemopericardium sufficient to cause cardiac tamponade in the absence of rupture of the heart or of a coronary artery. In the present communication we shall report three cases in which hemopericardium complicated acute myocardial infarction in the absence of rupture of the heart or of a coronary artery. One case is similar to others recently reported in that bishydroxycoumarin had been administered. In the other two cases anticoagulant therapy had not been employed. One of the latter two patients was demonstrated at necropsy not to have had a rupture of the heart or of a coronary artery. On the basis of the clinical course of the third patient, it is assumed that neither of these complications had occurred, although hemopericardium was demonstrated by pericardial tap.

REPORT OF CASES

CASE 1.—*Clinical Features.*—A 65-year-old woman was admitted to the hospital on April 18, 1950, with acute myocardial infarction. During the preceding three years she had been examined several times at the Mayo Clinic, at which times moderate elevation of blood pressure had been recorded.

Four days prior to her admission to the hospital, the patient had noted episodic dull substernal pain which extended to both shoulders and into both upper extremities. These attacks of pain would persist up to 30 minutes, unless she took glyceryl trinitrate (nitroglycerin) sublingually, which gave prompt relief. Intermittent pain of this type had occurred until the day of her admission, when the pain became severer and extended widely to the back, both arms, and the neck.

Physical examination at the time of the patient's admission to the hospital showed her to be restless, groaning, and complaining of severe pain. The blood pressure was 190 mm. of mercury systolic and 118 mm. of mercury diastolic. The pulse rate was 100 beats per minute. The cardiac rhythm was regular. Auscultatory examination of the heart and lungs revealed no significant abnormality. The peripheral pulses were all palpable and normal.

Dr. Anderson and Dr. Christensen are from the Division of Medicine, and Dr. Edwards is from the Section of Pathologic Anatomy, Mayo Clinic.

1. Goldstein, R., and Wolff, L.: Hemorrhagic Pericarditis in Acute Myocardial Infarction Treated with Bishydroxycoumarin, J. A. M. A. **146**:616-621 (June 16) 1951.

The immediate management included rest in bed and the administration of morphine sulfate and atropine sulfate by hypodermic injection and oxygen in an oxygen tent. Analysis of a specimen of urine showed the specific gravity to be 1.017. Albuminuria was graded 1 (on the basis of 1 to 4), glycosuria, 2, and microhematuria, 1. The value for hemoglobin concentration was 15 gm. per 100 cc. of blood; erythrocytes and leucocytes numbered, respectively, 4,760,000 and 11,100 per cubic millimeter of blood. Sedimentation of erythrocytes (Westergren method) was 30 mm. in one hour. Results of electrocardiographic study were consistent with the presence of extensive acute anterior myocardial infarction (Fig. 1). The values for urea and sugar were, respectively, 24 and 135 mg. per 100 cc. of blood.

On the morning after the patient's admission, anticoagulant therapy with bishydroxycoumarin was begun and was continued throughout her illness. The dosage schedule of bishydroxycoumarin, together with the values for prothrombin time, are listed in the Table. At no time did the deficit of prothrombin exceed a therapeutic range.

Anterior thoracic pain continued intermittently during the first five days of this patient's hospitalization, when it was not controlled by opiates. The pain was aching in character and was markedly aggravated by deep breathing and by turning. On the third hospital day the blood

Doses of Bishydroxycoumarin and Values for Prothrombin Time in Case 1

Date	Prothrombin Time, Sec.*	Bishydroxy-coumarin, Mg.	Date	Prothrombin Time, Sec.	Bishydroxy-coumarin, Mg.
4/19/50	..	200	5/ 1/50	34	75
4/20/50	49	..	5/ 2/50	38	50
4/21/50	34	75	5/ 3/50	32	75
4/22/50	37	50	5/ 4/50	38	50
4/23/50	..	50	5/ 5/50	39	50
4/24/50	33	75	5/ 6/50	28	75
4/25/50	30	75	5/ 7/50	..	75
4/26/50	27	100	5/ 8/50	34	50
4/27/50	41	..	5/ 9/50	31	75
4/28/50	31	75	5/10/50	45	..
4/29/50	26	100	5/11/50	..	..
4/30/50	..	50	.....	..	..

* Normal range for prothrombin time is 17 to 19 seconds. Infarction occurred on April 18, 1950; death on May 11, 1950.

pressure was 122 mm. of mercury systolic and 86 mm. of mercury diastolic and was approximately 100 systolic and 80 diastolic during the rest of her life. Repeated examination failed to reveal a pericardial friction rub at any time. At times, transitory rales could be detected at the pulmonary bases. Three roentgenograms of the thorax made with a portable machine showed scattered areas of increased density in the middle part of the right hemithorax suggestive of focal pneumonia.

The patient had mild fever, with daily peaks of temperature from 99.8 to 101.8 F. for 20 days. Thereafter the temperature was normal. The pulse rate ranged from 90 to 120 beats per minute. Convalescence was considered to be satisfactory, although improvement was slow.

Thirteen days after this patient's admission, precordial aching recurred, the pain of which extended in to the left arm. This aching was only partially relieved by morphine sulfate injected hypodermically.

In the forenoon of the 23d day anterior thoracic pain again developed, and the patient was noted to have mild cyanosis of the lips. Later on the same day, while using a bedpan, the patient became markedly cyanotic and dyspneic and died in a few minutes. The day of death was May 11, 1950.

Pathologic Features.—The pertinent necropsy observations concerned the heart and pericardium. Before the pericardium was opened, it was observed to be distended and purple. When it was opened, the pericardium was found to contain, under pressure, approximately 200 cc. of blood which, for the most part, was clotted (Fig. 2*a*).

The heart weighed 350 gm. External examination revealed that the apical third of the left ventricle had a discolored red and purple surface and bulged in an aneurysmal manner. Also, anteriorly there was an area of hemorrhage 1.5 by 1 cm. involving the epicardium over the ascending aorta and pulmonary trunk (Fig. 2*b*).

A tear in the epicardium could not be identified as a source of the hemopericardium. When the heart was opened (Fig. 2*c*), it was evident that there was a large transmural infarct involving the anterior wall of the left ventricle, the lower third of the ventricular septum, and all aspects of the apex. At the very apical portion the wall of the left ventricle was extremely thin, being only about 5 mm. in thickness. As the area of infarction blended with the intact

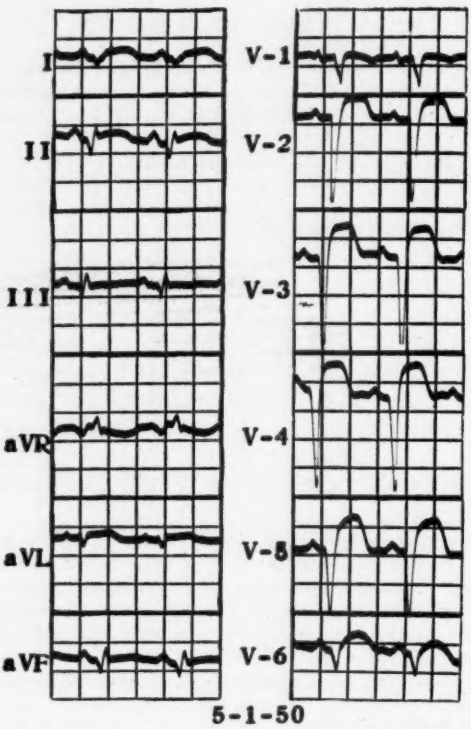

Fig. 1 (Case 1).—Electrocardiogram made two weeks after onset of the acute illness.

myocardium, necrotic muscle in the form of yellow material could be identified. The aneurysm evident from the exterior also was apparent when the heart was opened. It contained a large mural thrombus which was easily removed. After removal of the thrombus, inspection of the endocardium disclosed no tear. The coronary arteries showed many foci of severe degrees of narrowing by atherosclerosis. This narrowing was particularly prominent in the proximal third of the anterior descending coronary artery, where grossly no lumen could be identified. Microscopically, a small lumen was seen in this region. No thrombus could be observed in the vessels supplying the infarcted area, nor could rupture of a coronary artery be found. The valves were essentially normal.

The only observations of significance in the remainder of the necropsy were the presence of 1,000 cc. of clear fluid in each pleural cavity and atelectasis of the lower lobe of the right lung.

Microscopic examination of the heart showed, at the thinnest portion of the left ventricle, that all the muscle had been removed, leaving only condensed stroma. In these regions there were

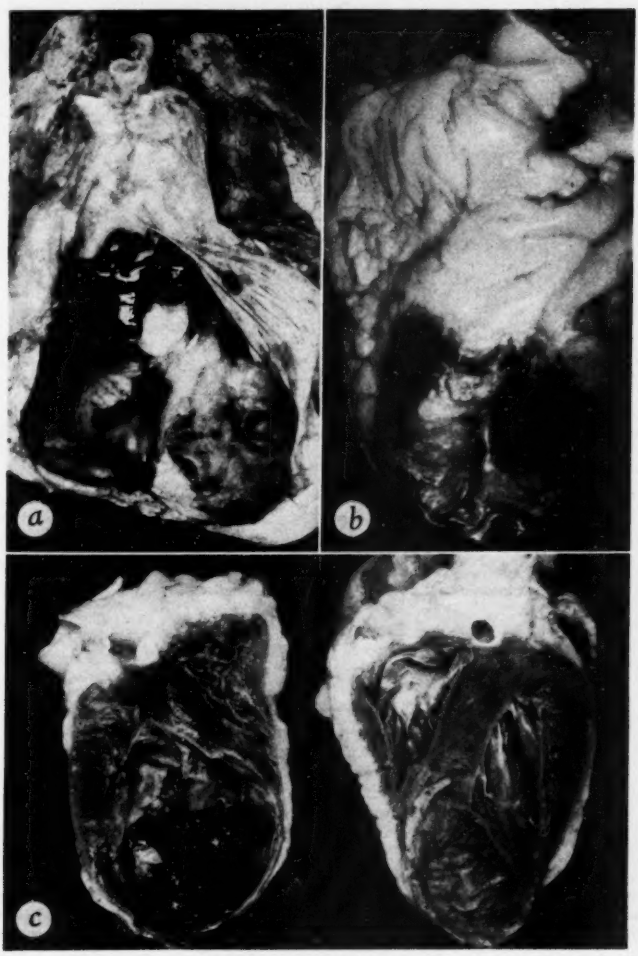

Fig. 2 (Case 1).—(*a*) The pericardial sac contains blood, some of which is clotted. (*b*) Anterior wall of the heart, showing discolored epicardium over anteroseptal infarct and also focus of hemorrhage in pericardium between pulmonary trunk and ascending aorta. (*c*) Heart opened by a longitudinal cut and in hinged fashion: anteroseptal myocardial infarction with thinning of wall and aneurysmal formation; mural thrombus in dilated apex.

small hemorrhages within the altered myocardium, the hemorrhages showing early organization. Over the area of greatest thinning of the myocardium, granulation tissue was growing from the epicardium into the pericardial cavity. In this tissue there were many foci of hemorrhage, giving the purple discoloration observed grossly (Fig. 3). In the epicardium, away from

the infarcted area, was a thin layer of vascular granulation tissue capped by a small amount of incompletely organized fibrin. Hemorrhage was not present in these areas. The area of infarction away from the apex revealed massive necrosis of myocardium, the process being surrounded on each side by myocardial stroma showing condensation and cellular infiltration, the cells consisting mainly of lymphocytes and macrophages. Pigment was present in the latter cells and was also free in the tissue. The capillaries in the stroma surrounding the infarct were wide and were associated with microscopic foci of hemorrhage.

The section taken from that intrapericardial portion of the ascending aorta which showed hemorrhage grossly revealed fresh hemorrhage into the epicardial tissues, but no overlying granulation tissue or surface hemorrhage.

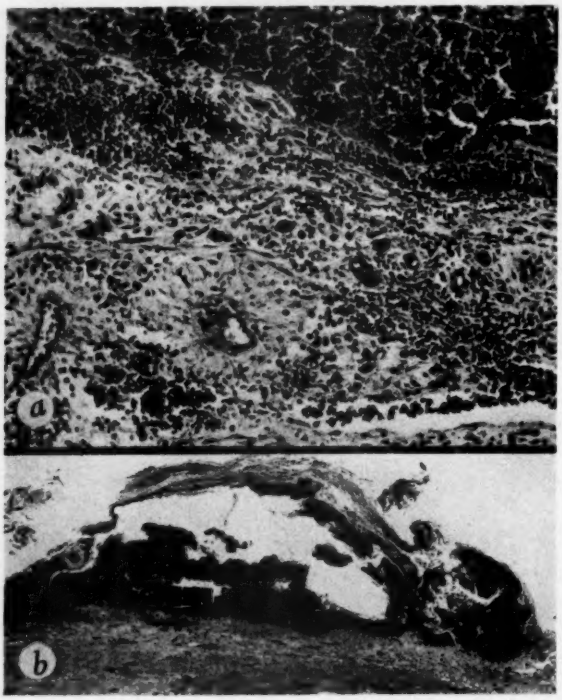

Fig. 3 (Case 1).—Photomicrographs of epicardium overlying anteroseptal myocardial infarct. (*a*) Granulation tissue containing many blood vessels; extravasation of blood into granulation tissue; hematoxylin and eosin stain; × 120. (*b*) Large focus of hemorrhage into epicardial granulation tissue; in this region, area of hemorrhage is still capped by granulation tissue; a small hemorrhage to the right appears to connect with the pericardial cavity; hematoxylin and eosin stain; × 7.

Microscopic examination of the liver showed central congestion without atrophy. The kidneys were normal. Microscopically, the lungs, in addition to involvement by atelectasis in the lower lobe of the right lung, showed congestion, edema, and focal hemorrhage.

Case 2.—*Clinical Features.*—A 57-year-old man was admitted to the hospital on Jan. 26, 1948, severely ill of congestive cardiac failure and recent left hemiplegia. The patient was known to have had hypertension and cardiac irregularity since 1945. During the six months before admission his physical effort had been curtailed by severe pain in the left arm induced

by exertion but relieved promptly by rest. Fifteen days before admission severe and constant pain had developed in the anterior portion of the thorax and in the left arm which persisted for 36 hours and which necessitated the use of three hypodermic injections of an opiate for relief.

He was then treated in another hospital for acute myocardial infarction, and progress was satisfactory for six days. Seven days before he came under our observation, pain in the left arm recurred. Shortly thereafter, he was observed to be mentally confused, to have difficulty in swallowing, and to be unable to move his left arm and leg. Left hemiparesis persisted; he continued to be disoriented. Persistent vomiting developed, with abdominal distention. These conditions were present when he came under our observation.

Physical examination disclosed obesity, mental confusion, dyspnea, irregularity of the pulse, with a rate of 100, weakness of the left facial muscles, and paralysis of the left arm and leg. The

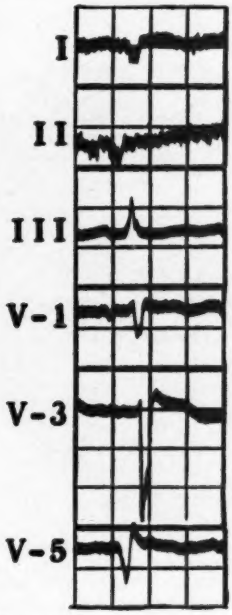

Fig. 4 (Case 2).—The electrocardiogram.

blood pressure was 126 mm. of mercury systolic and 76 mm. of mercury diastolic. Numerous moist rales were heard over the lower part of the thorax on the left. The liver was enlarged to palpation.

Results of urinalysis were normal. The value for hemoglobin concentration was normal. The leucocyte count was 12,000 per cubic millimeter of blood. The value for urea was 96 mg. per 100 cc. of blood. The erythrocyte sedimentation rate was 69 mm. in one hour (Westergren).

Electrocardiographic examination revealed abnormalities indicative of recent anteroapical myocardial infarction (Fig. 4). Roentgenograms of the thorax showed marked enlargement of the cardiac silhouette and pulmonary congestive changes.

Anticoagulant therapy with bishydroxycoumarin was considered but was not instituted because of retention of urea and because of a recent cerebral hemorrhage or infarction. Therapy included the administration of digitalis, morphine, and aminophylline. The patient did not respond favorably. His condition deteriorated progressively, with increasing evidence of respiratory difficulty. He died on Jan. 30, 1948, which was 18 days after the first prolonged anginal seizure and 3 days after his admission to our care.

Pathologic Features.—Necropsy showed the pericardial sac to be obliterated anteriorly by delicate fibrous adhesions over an area about 12 by 10.5 cm. (Fig. 5). Elsewhere the cavity was distended with blood clots totaling about 200 cc. Removal of the blood clots disclosed the pericardial surfaces to be shaggy as a result of fibrinous deposits. Most of the diaphragmatic surface of the heart was purple. Similar discoloration was present over a small zone at the anterior portions of the ascending aorta and pulmonary trunk. Dissection of the heart revealed a large healing anteroseptal infarct which also involved the entire apical portion. The involvement of the ventricular septum was extensive in that its upper limit lay within 1.5 cm. of the most basal portion. A large mural thrombus lay in the left ventricle over the area of infarction. No tear in the epicardium or in the endocardium could be found. The coronary arteries were widely involved by atheromatous lesions which had caused marked luminal narrowing. At the origin of the anterior descending coronary artery, the lumen was occluded by a thrombus. No point of rupture of a coronary artery could be found.

Fig. 5 (Case 2).—Anterior aspect of unopened heart: diffuse fibrinous pericarditis, dilatation of anteroseptal region corresponding with location of infarction; small focus of hemorrhage in pericardium over aorta and pulmonary trunk. There is also a small focus of epicardial hemorrhage over apex of right ventricle. Epicardium of diaphragmatic surface of this heart (not illustrated in this picture) was purple and appeared hemorrhagic (Fig. 6).

The remainder of the necropsy revealed edema of the lungs and several infarcts involving the lower lobes of the lungs, the largest infarct being 6 by 4 cm. Associated with these were pulmonary arteries occluded with thrombotic material presumed to be emboli. Examination of the brain showed a thrombus in the right posterior cerebellar artery, and associated with this was acute infarction involving the right temporal, parietal, and occipital lobes.

Microscopic examination of cardiac tissue showed massive necrosis of muscle in the areas observed grossly to be infarcted. Peripheral to the necrotic muscle was loose stroma from which necrotic muscle had been removed. The histologic picture of the infarct was consistent with the clinical history that the infarct had been present for 18 days. Hemorrhage was not present in the myocardium. Microscopic examination of the diaphragmatic portion of the left ventricle disclosed a thick layer of vascular granulation tissue deposited upon the epicardial surface. Overlying the granulation tissue was a layer of organizing fibrin. In the superficial portion of the granulation tissue and in the overlying fibrin were many areas of extravasated blood (Fig. 6). A similar microscopic picture was observed in the visceral pericardium over the

aorta and in the parietal pericardium. Such lesions seemed to represent the source of hemorrhage into the pericardial sac. Upon the epicardium overlying the infarct and corresponding with the delicate adhesions observed grossly was vascular connective tissue consistent in appearance with recently organized fibrinous pericarditis. Hemorrhage was not present in these areas, however.

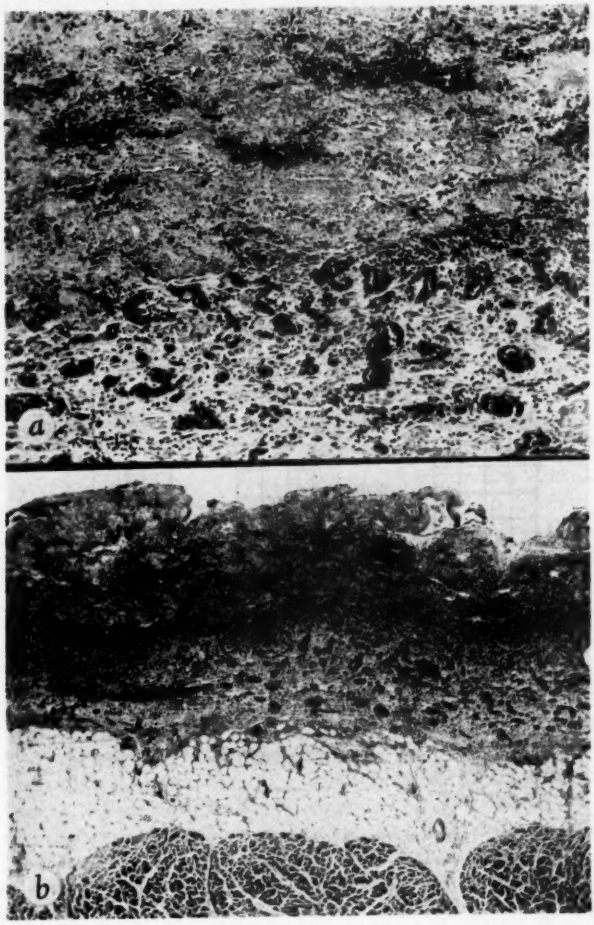

Fig. 6 (Case 2).—Photomicrographs taken from posterior wall of left ventricle in areas removed from location of the myocardial infarct. (*a*) Epicardial granulation tissue and overlying fibrin; vessels of granulation tissue are dilated; hemorrhages in granulation tissue; larger foci of hemorrhage into overlying fibrin; hematoxylin and eosin stain; × 95. (*b*) Epicardial granulation tissue and hemorrhage into overlying incompletely organized fibrin; hematoxylin and eosin stain; × 20.

The liver showed central congestion and mild central necrosis of the parenchyma. In the kidneys were focal hyalinized glomeruli but no other abnormalities. The spleen was congested.

Case 3.—A 60-year-old man was admitted to the hospital on July 23, 1950, for emergency treatment. For a week prior to admission he had had intermittent abdominal and lower

substernal pain. Four days prior to his admission, while he was at work with a jackhammer and laying tile pipe, severe pain developed in the lower anterior thoracic region; the pain was associated with dyspnea. The pain persisted and was aggravated by respiration, by swallowing, and by any movement. At no time did the pain extend into the neck or arms. Orthopnea and nocturnal dyspnea appeared and were so severe as to cause the patient to spend the two days and nights prior to his admission sitting in a chair.

Physical examination showed the patient to be critically ill. He was perspiring profusely and was markedly dyspneic and orthopneic. Blood pressure was 90 systolic and 70 diastolic, expressed in millimeters of mercury. The temperature was not elevated. Arterial pulsations in all extremities were weak and rapid but regular. The peripheral veins were distended.

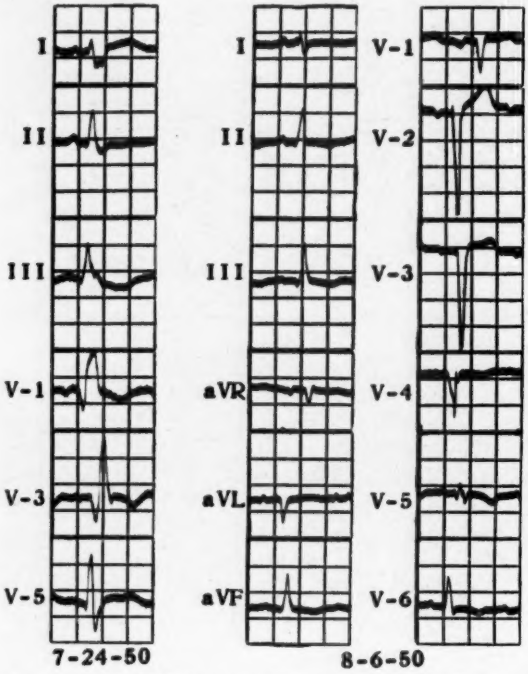

Fig. 7 (Case 3).—The electrocardiograms.

Cyanosis involved the face, head, and neck. Slight dulness, decreased breath sounds, and crepitant rales were noted over the pulmonary bases posteriorly. Cardiac dulness extended to the left anterior axillary line. The heart tones were faint. No cardiac murmurs were observed, nor was a friction rub or gallop present. There was no ankle edema.

Neither anemia nor polycythemia was present, but the patient had leucocytosis, as evidenced by a count of 13,000 cells per cubic millimeter of blood. The sedimentation rate (Westergren) was 22 mm. in one hour. Results of urinalysis were normal. A roentgenogram made with portable apparatus revealed marked enlargement of the cardiac silhouette and pulmonary congestion. An electrocardiogram showed a sinus rhythm, a rate of 88 beats per minute, and right bundle branch block. There were lengthened Q waves in Leads V_1 and V_6 (Fig. 7). The venous pressure in an arm was 281 mm. of water. The circulation time was prolonged (arm-to-tongue, 60 seconds; arm-to-arm, 70 seconds).

On admission the patient was placed in an oxygen tent. His condition remained critical. A Cheyne-Stokes type of respiration developed; the heart tones became fainter, and gallop rhythm was observed. Pericarditis of unknown origin was suspected at this point, though myocardial infarction remained a possibility.

Diagnostic and therapeutic pericardial tap was performed on the fifth hospital day. Fifty to 75 cc. of dark, bloody fluid was aspirated. Bacteriologic studies of the fluid subsequently were reported as giving negative results. Reevaluation led to a diagnosis of acute anteroseptal myocardial infarction, with hemopericardium and congestive heart failure.

The critical state of this illness was alleviated somewhat after the pericardial paracentesis. The patient gradually improved further after institution of a program which included the administration of digitalis and mercurial diuretics and the use of a diet low in sodium. Anticoagulant therapy was not employed. Serial electrocardiograms made during the course of the patient's illness are represented in Figure 7 and support the diagnosis of myocardial infarction.

On the 30th hospital day (Aug. 21, 1950) he was dismissed from the hospital to continue convalescent care at home.

During November, 1950, the bilateral "shoulder-hand syndrome" developed. During the middle of that month evidence of congestive cardiac failure reappeared. The latter complication responded favorably to treatment during a period of hospitalization. In December, 1950, at his request and when able, he was transferred to a Veterans Administration hospital for prolonged convalescent care. It was reported that, after leaving the care of the Veterans Administration hospital, he died in May, 1952, approximately 21 months after coming to our care because of acute myocardial infarction.

COMMENT

The pericarditis which occurs frequently in association with transmural myocardial infarction may well be likened to a granulating wound, in that a fibrinous exudate is present which undergoes organization, with proliferation of capillaries as healing progresses. In each of the two cases in which we carried out necropsy, gross extravasation of partly clotted blood was seen in the pericardial sac. Organizing fibrinous pericarditis, with hemorrhage into the granulation tissue, was present in each case. In neither was there rupture of the cardiac wall or of a coronary artery. In Case 1 the extravasation into the pericardial exudate coincided with the area of infarction, but in Case 2 the pericarditis over the infarcted myocardium was not hemorrhagic. Instead, hemorrhage in this case proceeded mainly into granulation tissue over the diaphragmatic surface, removed from the infarcted anterior wall of of the left ventricle. Hemorrhagic granulation tissue also was present over the parietal pericardium and in the visceral pericardium covering the ascending aorta.

Anticoagulant therapy with bishydroxycoumarin had been administered in each of the five cases of hemopericardium complicating myocardial infarction but without rupture of the heart or of a coronary artery that were reported by Goldstein and Wolff.[1] Similar therapy had been employed in a comparable case reported by Syner.[2] Bishydroxycoumarin therapy also had been given the patient with hemopericardium complicating nonspecific pericarditis described by McCord and Taguchi.[3] In the latter case necropsy showed the pericardial sac to be distended and tense with dark blood. The deficit of prothrombin produced by bishydroxycoumarin was considered to be a factor in producing the pericardial hemorrhage in each of the cases described in the reports cited.

2. Syner, J. C.: Extensive Pericarditis Complicating Myocardial Infarction, U. S. Armed Forces M. J. **3**:699-708 (May) 1952.

3. McCord, M. C., and Taguchi, J. T.: Nonspecific Pericarditis: A Fatal Case, A. M. A. Arch. Int. Med. **87**:727-731 (May) 1951.

Leedham and Orbison [4] described the development of hemopericardium in a patient with traumatic pericarditis, in whom it was considered that the heart had no point of rupture. These authors attributed the complication of hemopericardium in their patients directly to undesirably low levels of prothrombin activity resulting from anticoagulant therapy. In discussing the site of bleeding in their patient, who recovered after removal of 380 cc. of blood from the pericardium, these authors stated that

> . . . the major hemorrhage was incident to myocardial and pericardial softening during the evolutionary period, at which time the effect of dicumarol left the ends of small blood vessels inadequately sealed by protective clotting and allowed the occurrence of a massive hemorrhage.

It will be noted that bleeding from newly formed blood vessels, constituents of pericardial granulation tissue, was not suggested as a source of the hemopericardium although such a site is appropriately to be considered in their case. Such a view would be supported by the expressions of Goldstein and Wolff and by our observations; namely, that hemopericardium may result from bleeding pericardial granulation tissue. Goldstein and Wolff further pointed out that the trauma of the constantly moving heart coupled with the deficiency of prothrombin would seem to be additional factors stimulating bleeding at this site. It is of significance that of our three patients only one had received anticoagulant therapy.

Recently, pericardial hemorrhage and cardiac tamponade have been observed at necropsy at the Mayo Clinic in a 5½-year-old girl with a congenital ventricular septal defect after surgical exploration of the pericardial sac. In this patient the myocardium neither of the atria nor of the ventricles had been incised. The extravasation of blood arose from postoperative fibrinous pericarditis. This patient had received no anticoagulant therapy.

These observations indicate that hemopericardium may occur secondary to fibrinous pericarditis even in the absence of anticoagulant therapy. On hypothetical grounds the patient receiving anticoagulants, it should be admitted, would seem more likely to have the hemorrhagic complication than would the patient not receiving this type of therapy.

Patients who have extensive transmural myocardial infarction, in particular those in whom a pericardial friction rub is detected and especially those who are receiving anticoagulants, should be carefully observed in order to detect signs and symptoms of pericardial hemorrhage. Goldstein and Wolff have called attention to unusually long persistence or recurrence of the friction rub, recurrence of thoracic pain, and signs of inflow stasis as possible evidence of this complication. When bishydroxycoumarin therapy is being utilized and this complication develops use of that drug should be discontinued and neutralization of its effects with vitamin K_1 should be attempted. Signs of cardiac tamponade warrant pericardial paracentesis.

SUMMARY

Three patients who had acute myocardial infarction complicated by hemopericardium but without rupture of the myocardium or of a coronary artery are described.

4. Leedham, C. L., and Orbison, J. A.: Cardiac Tamponade Associated with Administration of Dicumarol, Circulation **1**:1065-1072 (April) 1950.

In two patients this complication contributed to a fatal outcome. The third patient, although critically ill, survived the episode of acute myocardial infarction and hemopericardium. Only one patient had received anticoagulant therapy (bishydroxycoumarin [dicumarol®]).

Organizing fibrinous pericarditis secondary to acute transmural myocardial infarction was demonstrated as the source of the hemorrhage into the pericardial sac in the two cases in which necropsy was done. In one of these cases the hemorrhagic process arose in the organizing pericarditis overlying the infarct, and in the other case bleeding arose from pericarditis in areas removed from the infarcted myocardium.

Hemopericardium, when suspected, requires prompt institution of anticoagulant-neutralizing measures if anticoagulant therapy has been used. Pericardial paracentesis may be a lifesaving measure when cardiac tamponade from hemopericardium occurs in the absence of a cardiac rupture.

ENTEROCOCCAL ENDOCARDITIS

THOMAS N. JAMES, M.D.
DETROIT

ONLY since bacterial endocarditis has become a treatable disease has its precise etiological classification assumed clinical importance. Although use of penicillin has reduced cases of the refractory disease to a minority, little headway has been made with this small group. It has become apparent that many penicillin-resistant cases are due to one of the enterococci.[1]

What fraction of these is caused by such organisms, streptococci of Lancefield Group D, is difficult to state, for until very recently most blood cultures have not been routinely investigated far enough to assure whether a yielded organism was an Enterococcus or not. Of greatest significance in this regard are the hemolytic properties of these bacteria: They may be alpha, beta, or gamma hemolytic, most commonly the last. Thus, when an alpha hemolytic Streptococcus has been isolated, identification has seldom been pressed further, a serious omission with a resistant organism.

Bacteriological characteristics of the Enterococcus group have been well described elsewhere.[2] Once the fact is kept in mind that any type of hemolysis may occur, identification becomes relatively simple. Two distinguishing properties commonly employed are their facile growth in 6.5% saline-lactose agar at 20 C. and their ability to reduce methylene blue in milk.

Clinical characteristics often suggest the correct diagnosis. Unlike most streptococci, the Enterococci are pus-formers and are frequently associated with metastatic abscesses. Infection with these organisms is viciously resistant to conventional therapy and often fails to respond from the onset; even when initial response is

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2. Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunity, Ed. 3, Baltimore, Williams & Wilkins Company, 1946. Flanders, J. F.; McGee, L. C., and Scott, E. G.: Enterococcal Endocarditis: Report of a Case Treated with Aureomycin, Ann. Int. Med. **36**:1323, 1952.

good, the rate of relapse is high and the development of resistance is rapid.[3] Positive blood cultures are the rule, and the ease with which they are obtained, as well as the persistence of bacteremia after conventional therapy, may assist in diagnosis.

With the diagnosis established, the treatment of enterococcal endocarditis still poses a problem. Robbins and Tompsett [4] were the first to emphasize the efficiency of combined penicillin and streptomycin therapy. Hunter [5] has offered corroboration for this clinical impression with some ingenious in vitro studies. He inoculated clots of blood, immersed them in various antibiotic solutions, and at various intervals ground up these clots and recultured them. It was Hunter's conclusion that a combination of penicillin and streptomycin was most effective in killing enterococci.

The eradication of enterococcal foci is also important.[6] The ubiquity of the enterococci, which inhabit the entire gastrointestinal and genitourinary tracts, makes the search for foci tedious. Robbins and Tompsett concluded that in men the commonest source was the urinary tract, particularly after urological procedures; in women the reproductive tract was the usual portal of entry, especially after abortion or septic delivery.

The purpose of this report is to present two cases of subacute enterococcal endocarditis successfully treated and to describe the treatment used, including some new aspects.

REPORT OF CASES

CASE 1.—A. B., a 32-year-old Negro housewife, was first seen on Nov. 6, 1951, complaining of a cough, asthenia, malaise, an upper respiratory infection, and a 10-lb. (4.5-kg.) weight loss. Her temperature was 100.8 F.; the blood pressure was 140/70, and the pulse rate was 120 per minute. A loud systolic murmur was transmitted over most of the precordium. The hemoglobin concentration was 7.1 gm., with a red blood cell count of 3,100,000 and a white blood cell count of 8,500, with 86% polymorphonuclear cells, 12% lymphocytes, and 2% eosinophiles.

The following features were significant in the past history: tonsillitis one year previous to admission which was treated conservatively; miscarriage six months later with loss of "a lot of blood"; fever and weight loss for the past six weeks; a cold for the preceding two days, with aggravation of the aforementioned general symptoms. The heart had been examined twice, four and two years previously, and no murmur was heard either time. There was no history suggesting rheumatic fever.

Hospital Course.—After her admission to the hospital on Nov. 7, her temperature ranged near 102 F. for six days. On Nov. 11 administration of 400,000 units of aqueous penicillin procaine was begun intramuscularly four times daily. Treatment was started with ferrous sulfate orally because of the anemia, but she was also given 500 cc. of whole blood. The blood culture on Nov. 8 yielded Streptococcus viridans, and on Nov. 12 intravenous administration of penicillin (5,000,000 units of 1,000 cc. of 5% dextrose solution in distilled water, twice daily) was begun, with almost immediate defervescence.

3. Leaman, W. G.; Wikingsson, M. B.; Webster, M. B., and Shaw, C. C.: Caronamide and Penicillin in Subacute Bacterial Endocarditis Due to Streptococcus Fecalis, Ann. Int. Med. **30**:646, 1949. Geraci, J. E.: Antibiotic Therapy of Bacterial Endocarditis: I. Experiences with Terramycin in the Treatment of Subacute Bacterial Endocarditis, Proc. Staff Meet., Mayo Clin. **27**:169, 1952.

4. Robbins, W. D., and Tompsett, R.: Treatment of Enterococcal Endocarditis and Bacteremia, Am. J. Med. **10**:278, 1951.

5. Hunter, T. H.: Treatment of Some Bacterial Infection of the Heart and Pericardium, Bull. New York Acad. Med. **28**:213, 1952.

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On Nov. 21 penicillin, 800,000 units four times daily, was again administered by the intramuscular route. That same day fever recurred, and the patient complained of sudden pain in the left upper abdominal quadrant; although the spleen was not palpable, the area was tender. On Nov. 23 intravenous administration of penicillin, 5,000,000 units daily, was resumed because of another positive blood culture. The organism grew profusely in 6.5% saline-lactose agar and was identified as an Enterococcus. The fever did not abate, and two days later the penicillin dose was doubled. Studies on the cultured organism showed greatest sensitivity to terramycin and bacitracin. Carinamide was employed in an effort to raise the penicillin blood level, but the determinations of levels were so variable that they were not useful. On Nov. 29 a small tender area appeared over the bicipital groove of the right humerus. Fifty milligrams of heparin was added to each unit of solution given intravenously in an attempt to maintain patency of the vein lumen. On Nov. 30 the penicillin dose was increaed to 10,000,000 units twice daily. The same day there was sudden pain in the right flank with deep tenderness in this area.

On Dec. 1 oral therapy with terramycin (1 gm. four times daily) was begun. After almost a month of oral administration of ferrous sulfate, the hemoglobin concentration was only 9.1 gm.; therefore, replacement therapy was begun with 250 cc. of packed red cells given on Dec. 3. Penicillin was still being given intravenously, and on Dec. 3 the first of many subsequent intravenous polyethylene catheters was inserted. The next day intravenous therapy with penicillin and oral administration of carinamide were discontinued, although the intravenous use of dextrose solution and oral treatment with terramycin were continued.

On Dec. 6 she was given two transfusions of 250 cc. of packed red cells. On Dec. 8 the hemoglobin concentration was 13.3 gm.; the white blood cell count was 12,400, with 17% polymorphonuclear cells, 25% lymphoctyes, and 4% eosinophiles. That same day terramycin (500 mg. twice daily) was included in the two 1,000-cc. intravenous dextrose infusions; oral administration of terramycin was discontinued. On Dec. 9 the fever began to subside for the first time since Nov. 21. Two days later she had acute pain in the left great toe, which was very tender. On Dec. 19 she had been afebrile for several days but began to have diarrhea and tenesmus. This was attributed to terramycin, which is largely excreted in the biliary tract and thence through the intestines, where it may act as an irritant. These symptoms were controlled with use of liquid petrolatum.

After subsidence of pain in the left great toe, the patient had pain in the left calf periodically, and by Jan. 3, 1952, the left foot was colder than the right. No left dorsalis pedis or posterior tibial pulse could be felt, although the artery was easily palpable and cord-like.

She remained afebrile, and on Jan. 15 the terramycin dosage was diminished by half; terramycin therapy was discontinued two days later because of severe thrombophlebitis, the first encountered in more than a month of intravenous injection of the antibiotic. On Jan. 22 the patient had a toothache, and the same day a positive blood culture was obtained, the first since Nov. 25, 1951. Dental examination revealed gingival calcareous deposits; dental roentgenograms disclosed a periapical abscess and several devitalized teeth. Intravenous administration of terramycin was resumed Jan. 23, and two days later, with continuous intravenous therapy, six teeth were extracted. Blood culture that day, as well as a culture of the periapical abscess, yielded enterococci. On Jan. 27 a cellulitis developed at the site of the venoclysis, and because of this the polyethylene catheter was removed the next day, three days after the dental extractions. One day after the catheter was removed, the fever returned for the first time since Dec. 9, 1951, despite the intercedent bacteremia. On Jan. 30 the intravenous therapy with terramycin was resumed, but the fever persisted. On Feb. 6 intramuscular administration of dihydrostreptomycin (1 gm. twice daily) was begun; terramycin therapy was discontinued because the vein thrombosed. Defervescence began again Feb. 7. On Feb. 9 an intravenous polyethylene catheter was reinserted, and intravenous administration of penicillin (10,000,000 units twice daily) in dextrose solution in water was resumed. On Feb. 11 two remaining devitalized teeth were extracted. None of the extractions was accompanied with undue bleeding, although 50 mg. of heparin was used in each 1,000 cc. of solution given intravenously; the menses, however, were unusually heavy each month while she received heparin.

On Feb. 20 the patient's temperature abruptly rose to 102 F. For the next five days fever persisted, the temperature once reaching 104 F. On Feb. 21 bacitracin therapy (15,000 units intramuscularly every six hours) was begun, but, when fever persisted three days later, use of this drug was discontinued. On Feb. 23 terramycin (1 gm. daily) was added to the solution

given intravenously. During this crisis, the patient insisted that she only had the "flu"; she pointed out that she ached all over and had a cold (which she did). There was an epidemic of influenza in the city at that time. On Feb. 25 the temperature returned to normal. Four blood cultures made during this febrile crisis yielded no pathogens.

She remained afebrile until March 5, when all antibiotic therapy was discontinued. Menses began March 6 and were normal in amount for the first time since she was hospitalized. It was also the first time she was not receiving intravenous heparin solutions. She continued to be afebrile, and on March 10, 1952, she was discharged from the hospital with ferrous sulfate and phenobarbital as her only outpatient medicaments. Her hematocrit reading at the time of discharge was 43 mm.

Pertinent Laboratory Data.—Five nonprotein nitrogen determinations, made before and after the nephrotoxic medications, were normal. Fasting blood sugar was normal, as were two

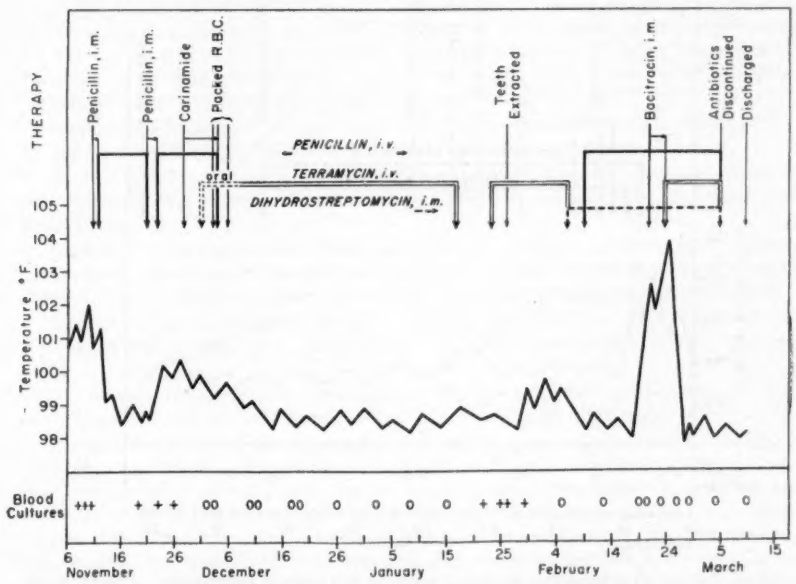

Chart 1 (Case 1).—Summary of case of subacute enterococcal endocarditis. Patient A. B. was a woman aged 32 (510067).

electrocardiograms. The Kline exclusion test was negative. Results of cephalin-cholesterol-flocculation, thymol turbidity, and thymol-flocculation liver-function tests were normal. Sensitivity tests done on three blood cultures and the tooth culture all revealed maximal sensitivity to terramycin and least sensitivity to penicillin and dihydrostreptomycin singly; in tube-dilution sensitivity tests, as described by Robbins and Tompsett, a combination of penicillin and dihydrostreptomycin afforded excellent bacteriostasis. Urinalyses gave normal results except when the patient was receiving carinamide or bacitracin, at which times she had albuminuria. Carinamide also caused hematuria, while bacitracin therapy was accompanied with pyuria and the passage of numerous casts. Urine cultures were negative. Warm-stage stool examinations gave negative results. Two chest roentgenograms failed to reveal abnormalities. Cardiac fluoroscopy demonstrated a prominent main pulmonary artery and slight right ventricular enlargement. Audiograms made before and after dihydrostreptomycin therapy were normal and did not change.

This patient has been followed six months as an outpatient and has remained afebrile and asymptomatic. Blood counts and cultures have been obtained each month, and anemia has not recurred; cultures have all been negative. The pulses in the left foot have gradually returned.

Comment on Case 1.—In retrospect, a number of things should have been done differently. The organism should have been identified fully, beyond its blood agar characteristics, from the first positive culture. Intravenous penicillin and intramuscular streptomycin therapy should have been the original antibiotic program. The anemia should have been corrected more promptly. A search for foci of infection should have been carried out earlier, using particularly dental roentgenograms. An intravenous polyethylene catheter should have been employed for the penicillin administration from the first.

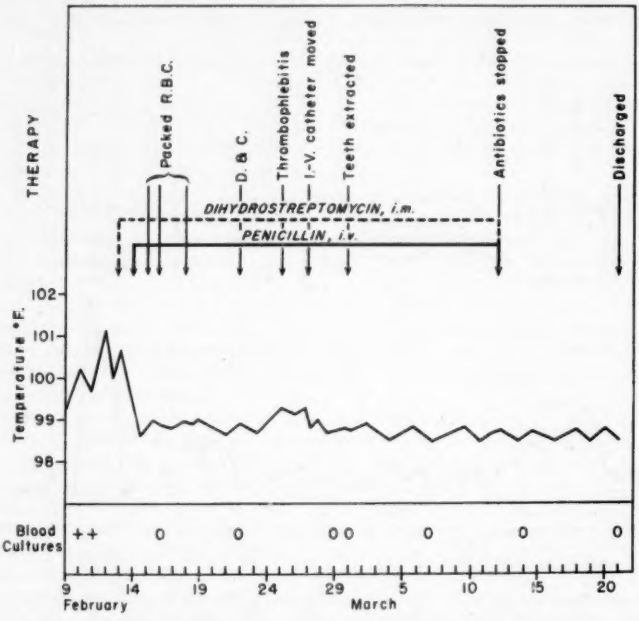

Chart 2 (Case 2).—Summary of case of subacute enterococcal endocarditis. Patient N. H. was a woman aged 30 (669773).
D. & C. indicates dilatation and curettage of uterus.

In this case terramycin probably exerted no appreciable bactericidal effect. Its bacteriostasis was deceiving for six weeks. In January positive blood cultures were obtained even when terramycin was being administered.

The enterococcus was identified by the usual characteristics and grew profusely in 6.5% saline-lactose agar. It did not liquefy gelatin and was classified as Streptococcus faecalis.

CASE 2.—N. H., a 30-year-old housewife, became ill in mid-December, 1951, at which time she had malaise, asthenia, a nonproductive cough, feverish sensation, and mild dyspnea on exertion. Her temperature in the evenings reached 103 F. The menses in December were unusually heavy, and an intermittent brown vaginal discharge persisted afterward. She lost 8 lb. (3.6 kg.) in the month prior to admission. There was no history suggestive of rheumatic fever. Her local physician treated her with periodic injections of penicillin, as well as with aureomycin orally, but the fever persisted. For three weeks before admission she had deep aching in the arms and legs.

She was admitted to the hospital on Feb. 9, 1952, appearing chronically ill but not in acute distress. Her temperature was 101 F.; the pulse rate was 104 per minute, and the blood pressure 118/82. The uterus was slightly enlarged. A Grade III systolic murmur was loudest along the left sternal border in the third to fifth intercostal spaces, but was also very loud over the dorsal portion of the spine. The aortic second sound was accentuated. Petechiae were sought, but none were found. The hemoglobin concentration on admission was 8.4 gm., with 2,500,000 red blood cells.

Hospital Course.—For the first four days the temperature ranged from 99 to 101.6 F. On Feb. 12, the fourth hospital day, an Osler node appeared in the third finger of the right hand, and there was also a petechia in the left lower conjunctiva. Later the same day a pelvic examination was done, and the possibility of an infected intrauterine polyp or abscess was established. On Feb. 13 the blood culture of Feb. 10 was reported as positive for Enterococcus. That same day intramuscular injection of dihydrostreptomycin (1 gm. twice daily) was begun. The next day administration of penicillin, 20,000,000 units per day in 5% dextrose solution in distilled water, was started with the use of an indwelling intravenous polyethylene catheter; 50 mg. of heparin was added to each 1,000 cc. of solution. Defervescence was almost immediate. On Feb. 15, 16, and 18, she received 250 cc. of packed red blood cells daily. Throughout the remainder of the hospitalization there were no more positive blood cultures. The hemoglobin concentration after transfusion was 13.6 gm., with 4,360,000 red blood cells.

Dental roentgenograms were made Feb. 20 and revealed a periapical abscess of the mandibular right central incisor; the right mandibular first molar was devitalized.

On Feb. 22 uterine dilatation and curettage were performed. Special culture was made of the endometrium but yielded no bacteria. Histopathological examination revealed endometrial hyperplasia.

On Feb. 25 a mild periphlebitis developed at the site of the intravenous catheter. When a new catheter was inserted in the other arm, the low-grade fever which had appeared promptly subsided. Two days later the dihydrostreptomycin dosage was reduced to 0.5 gm. twice daily.

On March 1 the two diseased teeth were extracted. The incisor was dipped in alcohol and then flamed before immersion in culture broth. It yielded a profuse pure culture of Enterococcus.

All antibiotic therapy was discontinued March 12. The patient remained afebrile and went home March 21, with elixir of ferrous sulfate as her only outpatient medicament.

Pertinent Laboratory Data.—The Kline exclusion test gave negative results. Results of urinalysis, the nonprotein nitrogen, and fasting blood sugar levels, an electrocardiogram, and a chest roentgenogram were all normal. Routine sensitivity tests (plate method) revealed maximal sensitivity to aureomycin and resistance to penicillin and dihydrostreptomycin separately. Again with the tube-dilution tests on these two drugs in combination, sensitivity to the combination was demonstrated. Audiograms made before and after dihydrostreptomycin therapy were normal and did not change. Cardiac fluoroscopy demonstrated increased prominence and pulsation of the main pulmonary artery, an enlarged left auricle, enlarged left ventricle, and right lateral scoliosis of the dorsal spine. The Enterococcus in this case did liquefy gelatin and was classified as Streptococcus liquefaciens.

This young woman has now been followed as an outpatient for six months, with monthly complete blood counts and blood cultures. There has been no recurrence of the anemia, no leucocytosis, and no positive blood culture. The second month there developed a trace of ankle edema, slight tenderness in the right upper abdominal quadrant, and a few moist rales at both lung bases; subjectively she complained of substernal aching, constantly present. All these symptoms and findings subsided with digitalization.

Comment on Case 2.—As a means of contrasting a random and a planned approach to the same problem, it was fortuitous that these two women were hospitalized in sequence. The difference in morbidity was striking. In the second patient the organism was identified earlier, the anemia was corrected more promptly, the focus of infection was identified and eradicated, combined penicillin and dihydrostreptomycin therapy was instituted from the outset, and a polyethylene catheter was used for the administration of all the penicillin intravenously.

GENERAL COMMENT

Although both of these patients had recently antecedent symptoms referable to the reproductive tract, in Patient A. B. a gynecological consultant after two examaminations was convinced that there was nothing suggesting uterine disease at the time of her hospitalization, and in Patient N. H. there was intrauterine disease, but the negative endometrial culture and the nonspecific histological changes of the curetted endometrium suggested that the uterine disease was functional rather than organic.

Judging from experience with these two patients, the teeth must be considered as a potential focus of infection whereby enterococci may enter the blood stream. Both patients had periapical abscesses, and the teeth in both cases yielded pure cultures of Enterococcus. Extraction of the diseased teeth undoubtedly contributed to the recovery of both patients. As a corollary to this finding, it seems reasonable to consider giving penicillin and streptomycin combined in antibiotic prophylaxis for extraction, rather than penicillin alone.

Correction of the anemia was instrumental in the successful therapeutic program in both patients. Both had blood-loss anemia and may eventually have responded to oral medication with iron preparations; the presence of infection added a separate factor, however, which no doubt impaired normal hematopoiesis. The anemia in turn aggravated the infection, completing a vicious cycle. Transfusion seemed the best means of breaking the cycle, and, in view of the heart disease in both patients, the smallest volume for the most hemoglobin and/or erythrocytes seemed preferable. For such a purpose packed red blood cells are ideal.

The routine use of an intravenous polyethylene catheter is recommended whenever protracted intravenous therapy is planned. If the solution being given intravenously is not allowed to run out without prompt replacement and if small amounts of heparin are added to each 1,000 cc. of solution, the catheter should remain patent for 10 to 14 days. This amount of heparin (about 50 mg. per 1,000 cc. of solution) obviated intracatheter clotting without exerting significant systemic effect on coagulation. Both patients experienced a slight increase in their menstrual flow during heparin therapy, but the hemograms were not altered significantly. In neither patient was there any abnormal bleeding associated with the dental extractions.

Intramuscular injections in the patient with enterococcemia should be kept at a minimum because of the organisms' proclivity for forming abscesses. This makes the intravenous route for penicillin administration more reasonable, particularly since experience has indicated the advisability of large doses of penicillin in this disease.

Studies are now being carried out to determine how many of the bacteremias occurring commonly after dental extraction are due to Enterococcus.

SUMMARY AND CONCLUSIONS

Two cases of successfully treated enterococcal endocarditis are presented.

Penicillin and streptomycin are recommended as the antibiotics of choice.

Dental infections are foci from which enterococcemia may originate.

Use of an indwelling intravenous polyethylene catheter is recommended when prolonged intravenous therapy is planned.

LACK OF INFLUENCE OF PENICILLIN ON BLOOD COAGULATION

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MILWAUKEE

THE REPORT of Moldavsky, Hasselbrock, and Cateno [1] that penicillin hastened the coagulation of blood has been confirmed by some workers and denied by others. The work of Macht [2] and the clinical impressions of Kemler,[3] Ochsner and DeBakey,[4] Frada,[5] and Pelz [6] supported the original findings, while the studies of Lewis,[7] Weiner, Zeltmacher, and Shapiro [8] and Dolkart and co-workers,[9] Fleming and Fish,[10] and Szczeklik and co-workers [11] failed to demon-

This study was aided by a grant from Chas. Pfizer & Company, Inc., Brooklyn 6.

From the Milwaukee County General Hospital and the Department of Medicine of Marquette University Medical School.

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11. Szczeklik, E.; Gibinski, K.; Kedra, M., and Kowarzykowa, Z.: Influence de la pénicilline sur les éléments morphotiques et les propriétés physiques du sang chez l'homme, Sang **20**:138-152, 1949.

strate a significant effect on any of the coagulation mechanisms tested. Observations of Hines and Kessler,[12] Axtrup,[13] and Lewitus[14] that in certain instances penicillin actually inhibited certain phases of coagulation have not been confirmed by other workers.[9c]

Although editorials and review articles have emphasized that the question of an effect of penicillin on blood coagulation has yet to be settled, certain textbooks already have warned against the use of penicillin because of its supposed effect on coagulation.[15] The present study was done to determine for the first time in vitro and in vivo the possible effect of penicillin on the prothrombin consumption, protamine titration, labile factor, and thrombin of normal blood. In addition, an attempt was made to confirm studies that had shown an influence of penicillin on coagulation time, prothrombin time, and clot retraction.

MATERIALS AND METHODS

In all tests siliconized syringes and needles were used. Coagulation times were estimated by the Lee-White method. Two tubes were used for the in vitro experiments and three tubes for those done in vivo. The methods of Quick[16] were used for the determinations of prothrombin time, labile factor, action on thrombin, clot retraction, and prothrombin consumption. Since the latter four determinations are not generally used, the exact procedures will be detailed.

Labile Factor.—Nine-hundredth milliliter (0.09 ml.) of stored human plasma that had a prothrombin time of between 40 and 60 seconds was mixed with 0.01 ml. of the fresh deprothrombinized plasma that was to be tested. One-tenth milliliter of thromboplastin (difco®) and 0.01 ml. of calcium chloride were added. The clotting time of the mixture was measured in the same manner as in the determination of prothrombin time.

Antithrombin or Thrombin-Promoting Activity.—One-tenth milliliter of one-fifth strength thrombin (Parke, Davis & Company) was added to 0.2 ml. of oxalated blood, and the time it took the mixture to clot was measured with a stop watch.

Clot Retraction.—Blood was collected in siliconized tubes, cooled for 10 minutes at 3 C., and centrifuged at 800 rpm for five minutes. One milliliter of the supernatant plasma (which was rich in thrombocytes [platelets]) was transferred to small Wassermann tubes, and the beginning of the clot retraction was noted.

Prothrombin Consumption.—Two milliliters of blood was allowed to coagulate in three tubes in a water bath at 37 C. The first tube was centrifuged at 3,000 rpm for one minute. The prothrombin content of the serum in this tube was then determined by mixing 0.1 ml. of the deprothrombinized rabbit plasma, thromboplastin, calcium chloride, and serum. Fifteen minutes later the second tube was centrifuged for one minute, and the prothrombin time of the serum in it and in the first tube was determined. Forty-five minutes after the initial coagulation, a new determination of the prothrombin content of the two first tubes was done, and after 60

12. Hines, S., and Kessler, D.: The Effect of Penicillin on Heparin Tolerance, J. A. M. A. **128**:794-796, 1945.

13. Axtrup, S.: Hypoprothrombinemia in Penicillin Treatment of Acute Infections in Infants, Acta pædiat. **35**:351-354, 1948.

14. Lewitus, Z. A.: Prothrombinopenic Effect of Penicillin, Correspondence, Arch. Int. Med. **82**:625, 1948.

15. Antibiotics and Blood Coagulation, Editorial, J. A. M. A. **141**:924, 1949. Long, P. H.: Antibiotics and Blood Coagulation, Correspondence, ibid. **142**:49-50, 1950. Quick, A. J.: Antibiotics and Blood Coagulation, Correspondence, ibid. **142**:505, 1950. Seegers, W. H.: Influence of Certain Drugs on Blood Coagulation and Related Phenomena, Pharmacol. Rev. **3**:278-344, 1951. Antibiotics and Blood Coagulation, Editorial, New England J. Med. **246**:240, 1952.

16. Quick, A. J.: The Physiology and Pathology of Hemostasis, Philadelphia, Lea & Febiger, 1951.

TABLE 1.—*In Vitro Effect of Varying Concentrations of Penicillin on Coagulation Time, Labile Factor, Prothrombin Consumption, and Clot Retraction of Normal Blood*

Type of Determination	Concentration of Penicillin, γ/Ml.										
	0		1		5	50	100	200		400	
Coagulation Time, Min.											
1	9	..	..	..	8	8	..	9	..	9	..
2	8	..	..	..	8	8	..	8	..	8	..
3	10	..	..	..	10	10	..	10	..	11	..
4	11	..	..	..	11	11	..	11	..	11	..
5	10	..	..	..	10	10	..	10	..	10	..
6	10.5	..	..	..	..	..	10.5	10.5	..	10.5	..
7	10	..	..	..	..	..	11	11	..	11	..
8	10	..	..	..	..	..	10	10	..	10	..
9	10.5	..	..	..	..	..	10.5	10.5	..	12.5	..
10	10	..	..	..	..	..	10	10	..	10	..
										$P^* = 0.11$	
Labile Factor, Sec.											
1	17.7	..	..	..	..	..	..	..	..	17.5	..
2	20.5	..	..	..	..	..	..	..	..	20.5	..
3	19.7	..	..	..	..	..	..	..	..	19.5	..
4	20.0	..	..	..	..	..	..	..	..	20.5	..
5	18.3	..	..	..	..	..	..	..	..	18.4	..
6	16.3	..	..	..	..	..	..	..	..	16.3	..
7	18.5	..	..	..	..	..	..	..	..	18.6	..
8	18.5	..	..	..	..	..	..	..	..	18.6	..
										$P = > 0.05$	
Prothrombin Consumption, Sec.†	1	2	..	..	..	..	..	1	2	1	2
1	36	27	..	..	..	..	..	..	..	23	32
2	21	16	..	..	..	..	..	..	..	28	22
3	36	24	..	..	..	..	..	..	..	34	26
4	24	17	..	..	..	..	..	..	..	26	17.5
5	26	21	..	..	..	..	..	..	..	26	18
6	21.5	17	..	..	..	..	..	..	..	23	17.5
7	21	20	..	..	..	..	..	..	..	21	19.5
8	23.5	21.5	..	..	..	..	..	..	..	25.5	17.5
9	22	23	..	..	..	..	..	..	..	20.5	14
10	21.5	20	..	..	..	..	..	..	..	20	16.5
11	22	18	..	..	..	..	..	23	17	..	..
12	27.5	19	..	..	..	..	..	27.5	19.5	..	..
13	28	16	28	17	..	..	..	..	..	..	..
14	18	24	18.5	20	..	..	..	..	..	..	..
										$P = > 0.5$	
Clot Retraction, Min.											
1	12	..	14	..	..	..	13	13	..	15	..
2	21	..	20	..	..	..	20	15	..	15	..
3	13	..	13	..	..	..	13	13	..	13	..
4	12	..	13	..	..	..	15	12	..	12	..
5	16	..	14	..	..	..	12	12	..	13	..
6	16	..	16	..	..	..	16	16	..	16	..
7	17	..	18	..	..	..	17	17	..	17	..
8	13	..	16	..	..	..	14	14	..	14	..
9	17	..	17	..	..	..	17	17	..	18	..
										$P = > 0.5$	

* Values for P were determined throughout as outlined in Snedecor, G. W.: Statistical Methods, Applied to Experiments in Agriculture and Biology, Iowa City, The Iowa State Press, 1946. A value of 0.01 or less is necessary for results to be significant.

† In tables 1 and 3 the prothrombin content of the first two tubes is recorded 60 minutes after the initial coagulation in order to save space. These values are representative of the complete data.

minutes the third tube was centrifuged, and the prothrombin content of the three tubes was determined for the last time.

Protamine Titration.—The method of Allen[17] was used. To 10 tubes containing amounts of protamine sulfate ranging from 0.02 to 0.2 mg. in 0.02 to 0.2 ml. of distilled water, 1 ml. of heparinized blood was added. The end-point was represented by the tube with the least amount of protamine sulfate in which clotting took place. It was assumed that if penicillin had an antiheparin effect clotting would take place in the presence of decreased amounts of protamine. If it had a heparin-enhancing effect, a greater amount of protamine would have been necessary to allow coagulation.

In Vitro Experiments.—Blood was used from healthy student nurses. It was mixed with increasing amounts of penicillin by adding to 1 ml. of plasma 0.02 ml. of isotonic sodium chloride solution containing 1 to 400 γ of penicillin (Bristol Laboratories). These concentrations of penicillin were used in order to include the extreme levels of the drug that might be found in patients. Studies were done on the influence of penicillin on coagulation time, pro-

TABLE 2.—*In Vitro Effect of Varying Concentrations of Penicillin on Prothrombin Time and Thrombin Activity of Normal Blood*

Type of Determination	Concentration of Penicillin in the Blood, γ/Ml.										
	0	1	2	4	8	16	32	64	128	200	400
Prothrombin Time, Sec.											
1	12.4	12.5	12.0	12.2	12.1	12.1	12.3	12.2	12.4	12.0	12.6
2	12.2	12.5	12.0	12.0	12.2	12.2	12.2	12.1	12.2	12.2	12.5
3	12.1	12.2	12.2	12.1	12.0	12.1	12.3	12.1	12.3	12.3	12.3
4	12.3	12.4	12.2	12.5	12.3	12.3	12.3	12.2	12.1	12.1	12.2
5	12.0	12.0	12.0	12.1	12.0	12.1	12.1	12.1	12.1	12.0	12.0
											$P = > 0.5$
Action on Thrombin, Sec.											
1	7.2	7.3	7.2	7.0	7.1	7.0	7.1	7.3	7.6	7.4	7.9
2	6.9	7.3	7.2	7.3	7.8	7.1	7.1	7.3	7.2	7.2	7.1
3	7.9	8.0	8.0	8.0	8.1	7.7	8.2	8.1	8.0	7.9	7.7
4	7.0	7.2	7.0	7.3	7.3	7.3	7.0	7.4	7.0	7.2	7.2
5	7.4	7.5	7.3	7.5	7.5	7.5	7.3	7.4	7.3	7.5	7.4
6	8.0	8.1	8.0	7.8	7.9	7.8	7.7	7.6	7.8	7.9	7.8
7	6.6	6.6	6.8	6.7	6.8	6.8	6.8	6.7	6.5	6.6	6.8
8	6.8	6.7	6.6	6.8	6.7	6.6	6.6	6.7	6.6	6.6	6.8
9	7.0	7.2	7.3	7.3	7.0	7.0	6.7	7.2	6.6	7.0	7.1
10	6.9	6.9	7.0	6.9	6.8	6.9	7.0	7.0	7.0	6.9	6.9
											$P = 0.37$

thrombin time, action on thrombin, the labile factor, prothrombin consumption, heparin activity, and clot retraction.

In Vivo Experiments.—The subjects were physically normal male patients with mental disease and patients in the medical wards who did not have fever, liver disease, or any other impairment that might influence blood coagulation. The following procedure was used: Blood was drawn for determination of control values for coagulation time, prothrombin time, thrombin, labile factor, prothrombin consumption, and protamine titration. One million units of buffered crystalline penicillin in 20 ml. of sterile saline solution was then injected intravenously. Twenty minutes later blood was again drawn; the various tests were repeated, and the penicillin level was determined by the method of Rammelkamp.[18] Two hundred thousand units of penicillin was given intramuscularly every 4 hours for 24 hours after the initial injection. After a total of 2,600,000 units of penicillin had been given a third sample of blood was drawn and the tests

17. Allen, J. G.; Moulder, P. V.; Elghammer, R. M.; Grossman, B. J.; McKeen, C. L.; Sanderson, M.; Egner, W., and Crosbie, J. M.: A Protamine Titration as an Indication of a Clotting Defect in Certain Hemorrhagic States, J. Lab. & Clin. Med. **34**:473-476, 1949.

18. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**:95-97, 1942.

TABLE 3.—*In Vivo Effect of Penicillin on Coagulation Time, Prothrombin Time, Thrombin, Labile Factor, and Prothrombin Consumption of Blood*

Patient	Penicillin Level, γ/Ml.		Coagulation Time, Min.			Prothrombin Time, Sec.			Action on Thrombin, Sec.			Labile Factor, Sec.			Prothrombin Consumption, Sec.					
															Control		20 Min.		24 Hr.	
	20 Min.	24 Hr.	Control	20 Min.	24 Hr.	Control	20 Min.	24 Hr.	Control	20 Min.	24 Hr.	Control	20 Min.	24 Hr.	1	2	1	2	1	2
R. L.	..	...	12.5	12.5	14	12	11.5	11.4	7	7.5	7.5	....	....	....	..	..	..	..	..	..
A.	..	...	12.5	13	12.5	12	12	12	7.3	7.5	6.8	....	....	....	29	26	28	17.5	28	28
W. E.	..	...	12.5	14	....	12	12	....	7.0	7.1	...	....	....	....	30	31	34	20	27	33
B. H.	..	...	12	12.5	13.5	....	....	....	...	...	...	....	....	....	46	72	80	42	..	..
D. T.	..	...	16	15.5	....	....	....	....	7.2	7.0	...	....	....	....	..	..	..	..	..	..
F. M.	..	...	14.5	16	16	....	....	....	...	...	...	....	....	....	..	..	..	..	..	..
R. B.	..	...	16	16.5	....	12.5	12.5	....	6	6	...	....	....	....	..	..	..	..	..	..
F. C.	..	...	13	13	14.5	12.2	11	11	6	6	6.5	....	....	....	44	24	40	44	35	33
C. M.	..	...	14	14	13.5	11.3	11	11.6	6	6	6	....	....	....	15	27	21	27	22	27
F. V.	39	0.5	13	12	13	12.2	12	12.3	6.2	6.5	6.8	....	....	....	36	34	33	33	34	35
C. K.	153	...	12	10.5	11	11.5	11.7	12	7.5	7.8	7.7	23	23.5	23	30	22	27.5	25	..	..
M. M.	37	4	11.5	11.5	12	11.6	11.7	11	7.4	7.7	7.0	21	21.5	23	..	..	..	..	..	..
F. H.	37	0.5	12	11	12	11.8	11.9	12	6.7	6.8	7.2	....	....	....	..	..	..	..	..	..
R. G.	67	2	13.5	14	13.5	12	12.5	12.2	6.8	6.8	7.2	23	22	22	..	..	..	..	..	..
T. K.	37	0.5	12.5	13.5	14	12.1	12	11.6	7.0	6.5	6.8	23	23	23.5	..	..	..	..	..	..
W. W.	..	...	....	....	....	11	11	10.9	...	...	...	20.5	21	20	..	..	..	..	..	..
D. M.	..	...	....	....	....	11.6	12	12	...	...	...	19	19	18.5	..	..	..	..	..	..
J. G.	..	...	....	....	....	11	10.9	10.8	...	...	...	17	17.8	17	29	25	31	24	28	26
J. N.	..	...	....	....	....	11.3	11.3	11	...	...	...	16	16.7	16.9	35	42	38	40	34	43
C. L.	..	...	....	....	....	11.5	12	12.2	...	...	...	20	20.1	19.5	40	41	43	40	38	42
W. J.	..	...	....	....	....	12.5	12.5	12	...	...	...	19	19	20	22	30	22	22	21	32
B. C.	..	...	....	....	....	11.2	11.8	11.2	...	...	...	19.8	20.2	19.5	31	30	33	28	40	41
E. W.	..	...	....	....	....	11.5	12	12.5	...	...	...	18.2	18.7	19.5	40	35	41	37	40	34
J. N.	..	...	....	....	....	11.3	11.3	11	...	...	...	....	....	....	..	..	..	..	..	..
N			15	15	12	21	21	19	13	13	10	12	12	12	13	13	13	13	11	11
P			....	> 0.5	0.06	....	> 0.5	> 0.5	...	0.26	0.25	....	0.1	0.34	..	..	> 0.5		> 0.5	

of coagulation were repeated. In order to test the possible effect of the administration of penicillin over a longer period the prothrombin times were determined for 10 additional patients who had been receiving 400,000 units of penicillin per day for 3 to 15 days.

RESULTS

Coagulation Time.—In 10 in vitro experiments a concentration of 5 to 400 γ of penicillin had no significant effect on the coagulation time of the blood (Table 1). There was no significant difference between the control coagulation time and that determined 20 minutes and 24 hours after the injection of penicillin in 15 patients (Table 3). The concentration of penicillin in the blood of these patients ranged from 0.5 to 153 γ per milliliter (Table 3).

Prothrombin Time.—In five in vitro experiments concentrations of 1 to 400 γ per milliliter of penicillin did not have a significant effect on the prothrombin time of 14 patients (Table 3). Ten additional patients who had received penicillin for 3 to 15 days also had prothrombin times well within normal limits.

Action on Thrombin.—In 10 in vitro experiments concentrations of penicillin ranging from 1 to 400 γ per milliliter had no effect on thrombin activity in normal blood (Table 2). The blood of 13 subjects who were given penicillin showed no significant antithrombin or thrombin-promoting activity (Table 3).

Prothrombin Consumption.—Fourteen in vitro determinations failed to reveal any effect on prothrombin consumption of concentrations of penicillin ranging from 1 to 400 γ per milliliter (Table 1). In 14 patients the administration of penicillin had no demonstrable effect on the prothrombin-consumption values (Table 3).

Protamine Titration.—The titration was done on the bloods of eight patients before and after they received 1,000,000 units of penicillin by vein and after they had received 200,000 units of penicillin intramuscularly at four-hour intervals for one day. In each instance 0.08 gm. of protamine was necessary to inhibit the added heparin and to prevent clotting. Thus, the penicillin had no antiheparin or heparin-like effect.

Clot Retraction.—In 12 in vitro experiments concentrations of penicillin ranging from 1 to 400 γ per milliliter had no demonstrable effect on the length of time necessary for clot retraction to take place (Table 3).

COMMENT

The data gathered in this study failed to confirm studies and impressions that seemed to indicate penicillin would increase the coagulability of the blood.[19] In addition, the assertions that penicillin inhibited the clotting of blood[20] were not confirmed. The finding of Macht[2c] (shown in his Table 6) that amorphous penicillin increased coagulability, while crystalline penicillin did not, may explain the apparent discrepancy between our observations and other studies in which crude preparations might have been tested. The effects on coagulation formerly ascribed to penicillin may have been due to impurities present in the preparations available a few years ago.

19. Footnotes 1 to 6.

20. Footnotes 12 to 14.

SUMMARY AND CONCLUSIONS

Experiments were done in vitro and in vivo on the effect of varying concentrations of crystalline penicillin on the prothrombin time, coagulation time, thrombin, prothrombin consumption, labile factor, clot retraction, and protamine titration of normal blood.

It was shown for the first time that penicillin did not affect prothrombin consumption, labile factor, thrombin, and protamine titration. In addition, studies that had failed to show an effect of penicillin on the coagulation time, prothrombin time, and clot retraction of normal blood were confirmed.[21]

It seems likely that effects on blood coagulation that have been attributed to penicillin were due to impurities present in early preparations of this drug. Thus, it is concluded that when crystalline penicillin is used the possibility of an effect on blood coagulation need not be considered.

21. Footnotes 7 to 11.

LYMPH NODES IN RHEUMATOID ARTHRITIS

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SYSTEMIC involvement of lymphoid tissue is a well-recognized feature of rheumatoid arthritis.[1] Among patients with rheumatoid arthritis, 50 to 75% may be found to have palpable lymph nodes.[2] These nodes usually are painless, nontender, discrete, and movable under the skin. They may vary from small pea-sized structures to sizable lymph nodes (up to 3 cm.) which immediately attract clinical attention. They may be at the usual sites of clinically discernible lymph node enlargement, such as in the axillary, epitrochlear, cervical, and inguinal areas. Some patients, however, show enlarged lymph nodes at unusual sites, such as along the course of vascular channels of mid-arm or mid-thigh.[3] It is now generally believed[4] that the lymph node involvement represents participation of the lymphatic apparatus in the systemic disease, which rheumatoid arthritis is believed to be, rather than regional lymphadenopathy secondary to drainage from diseased joints. This belief

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2. (*a*) Chauffard, A., and Ramond, F.: Des adénopathies dans le rhumatisme chronique infectieux, Rev. med., Paris **16**:345, 1896. (*b*) Waterhouse, R.: The Superficial Lymph Glands in Rheumatoid Arthritis, St. Barth. Hosp. Rep. **43**:107, 1908. (*c*) Coates, V., and Delicati, L.: Rheumatoid Arthritis and Its Treatment, London, H. K. Lewis & Company, Ltd., 1931. (*d*) Bauer, W.: Personal communication to the authors, 1951.

3. Rotes Querol, J., and Ciscar Rius, F.: A propósito de un caso de enfermedad de Still-Chauffard en el adulto, con aspecto ganglionar histológico de linfoblastoma folicular, Med. clín., Barcelona **10**:167, 1948

4. (*a*) Farreras Valentí, P. F.: Tipos anatómicos de linfadenopatías con que la poliartritis crónica progresiva puede evolucionar, Rev. españ. reum. **2**:273, 1947. (*b*) Poursines, Y., and Rochu, P.: Étude histopathologique des adénopathies dans les rhumatismes articulaires chroniques, Rev. rhum. **13**:129, 1946. (*c*) Jiménez Díaz, C.; Morales Pleguezuelo, M.; de Oya, J. C.; Roda, E., and López García, E.: La naturaleza del llamado sindrome de Felty y afecciones similares: Reticulosis poliartritica, Rev. clín. españ. **23**:368, 1946.

is further strengthened by the finding that in up to 20% of patients with rheumatoid arthritis the spleen is palpable.[5] Our conclusions agree with this general impression. However, the possibility cannot be categorically denied that the enlarged lymph nodes, particularly at the more unusual sites, occasionally may be the result of drainage.

A study of lymph nodes in rheumatoid arthritis must make mention of Felty's syndrome and Still's disease (Still-Chauffard-Felty syndrome). Both are variants of rheumatoid arthritis with prominent involvement of the reticuloendothelial system.[6]

Felty's syndrome is characterized by classic symptoms of rheumatoid arthritis in adults accompanied with splenomegaly and leucopenia. Lymphadenopathy and mild normochromic or hypochromic anemia may or may not be present. Some authors question the existence of the entity believing that Felty's syndrome represents simply rheumatoid arthritis with coexistence of other diseases, leading to splenomegaly and leucopenia.[7] This undoubtedly is true in some instances. However, good evidence [8] supports the belief that many instances of Felty's syndrome represent rheumatoid arthritis with hyperreaction of the reticuloendothelial system and resultant splenomegaly. The blood findings are related to the yet unexplained mechanism by which splenomegaly often results in leucopenia and other cytopenias. In this connection the frequent finding of multiple joint involvement not always diagnostic of rheumatoid arthritis in patients with so-called primary splenic neutropenia should be mentioned.[9] The conditions of none of the patients studied by us fall into these categories.

Still's disease [10] is closely related to Felty's syndrome. This entity represents juvenile rheumatoid arthritis associated with splenomegaly and lymphadenopathy. Lymph node enlargement is often generalized in Still's disease, and the extent of lymphadenopathy and splenomegaly waxes and wanes with activity of the underlying arthritis. Splenomegaly and prominent lymphadenopathy in this disease may be explained by the usually more reactive lymphatic system in children. Still-Chauffard-Felty syndrome and its manifestations thus probably represent the same disease process as rheumatoid arthritis, with the distinction that lymphatic system involvement and splenomegaly are in the clinical foreground.[4c]

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5. (*a*) Ragan.[1] (*b*) Bauer.[2d] (*c*) Lockie, L. M.; Sanes, S., and Vaughan, S. L.: Chronic Arthritis Associated with Neutrophilic Leukopenia, Splenomegaly and Hepatomegaly, Am. J. Clin. Path. **12**:373, 1942.

6. Felty, A. R.: Chronic Arthritis in the Adult, Associated with Splenomegaly and Leucopenia, Bull. Johns Hopkins Hosp. **35**:16, 1924. Hutt, M. S. R.; Richardson, J. S., and Staffurth, J. S.: Felty's Syndrome: A Report of 4 Cases Treated by Splenectomy, Quart. J. Med. **20**:57, 1951.

7. Talkov, R. H.; Bauer, W., and Short, C.: Rheumatoid Arthritis Associated with Splenomegaly and Leukopenia, New England J. Med. **227**:395, 1942. Steinbrocker, O., and Sesit, M. F.: Chronic Rheumatoid Arthritis with Granuloma of the Spleen and Lymph Nodes in a Patient Presenting the Clinical Picture of Felty's Syndrome, New York J. Med. **40**:1795, 1940.

8. Jiménez Díaz and others.[4e] Lockie and others.[5c]

9. Wiseman, B. K., and Doan, C. A.: Primary Splenic Neutropenia, Ann. Int. Med. **16**:1097, 1942. Langston, W.; White, O. A., and Ashley, J. D.: Splenic Neutropenia: Report of a Case with Splenectomy, ibid. **23**:667, 1945.

10. Schlesinger, B. E.: Still's Disease: A Survey of Chronic Rheumatic Diseases, London, Oxford University Press, 1938.

Our interest in the pathology of lymph nodes in rheumatoid arthritis was aroused when lymph node biopsy specimens from several patients with this disease revealed lesions resembling giant follicular hyperplasia (Brill-Symmers disease, Table 2) [11] lymphosarcoma, and Hodgkin's disease. A search of the American literature failed to disclose any detailed studies on lymph node pathology in rheumatoid arthritis. We found, however, several papers in recent European literature commenting on the coincidence of rheumatoid arthritis and giant follicular hyperplasia.[12] Another study mentioned histologic similarities to Hodgkin's disease.[4b]

This study of the lymph node pathology in patients with rheumatoid arthritis was undertaken for the following reasons: (*a*) to delineate any specific histologic features of lymphadenopathy in rheumatoid arthritis and (*b*) to evaluate lesions resembling giant follicular hyperplasia and other malignant lymph node diseases in patients with rheumatoid arthritis.

TABLE 1.—*Lymphatic System Involvement in Rheumatoid Arthritis and Related Syndromes*

Rheumatoid arthritis
50-75% of patients may have palpable lymph nodes not necessarily related to involved joints
5-30% of patients may have palpable spleens
Still's disease
Rheumatoid arthritis + lymphadenopathy + splenomegaly; mostly in children; extent and severity of lymphatic system involvement usually paralleled by severity of articular disease
Felty's syndrome
Rheumatoid arthritis + splenomegaly + leucopenia; lymphadenopathy may be present; mild anemia may be present

TABLE 2.—*Characterization of Giant Follicular Lymphoblastoma (Brill-Symmers Disease)*

Features Present	Features Absent
1. Generalized lymphadenopathy due to marked hyperplasia	1. Abnormal cells in peripheral blood
2. Frequent splenomegaly	2. Anemia and cachexia
3. Multicentric origin	3. Articular symptoms
4. Marked radiosensitivity	4. Tonsillar involvement
5. Usually preneoplastic; followed by lymphatic leukemia, lymphosarcoma, or Hodgkin's disease after several years	5. Involvement of lymphatic apparatus of gastrointestinal tract

MATERIAL AND METHODS

Biopsies of lymph nodes were performed on nine patients with rheumatoid arthritis. In each instance the lymph nodes were palpably enlarged. Axillary, supraclavicular, epitrochlear, or cervical nodes were examined as indicated by the case reports. Laboratory studies performed included blood cell counts, Wintrobe sedimentation rates, serologic tests for syphilis, urinalyses, and total protein determinations (with chemical fractionations in some instances).[13] Electro-

11. Brill, N. E.; Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen, J. A. M. A. **84**:668, 1925. Symmers, D.: Giant Follicular Lymphadenopathy With or Without Splenomegaly, Arch. Path. **31**:385, 1942.

12. (*a*) Rotes Querol and Ciscar Rius.[3] (*b*) Footnote 4 *a* and *c*. (*c*) Parkes Weber, F.: The Nodules and Lymph Gland Enlargement in Rheumatoid Arthritis, Ann. Rheumat. Dis. **4**:3, 1944.

13. Wolfson, W. Q.; Cohn, C.; Calvary, E., and Ichuba, F. V.: Studies in Serum Proteins: Rapid Procedure for Estimation of Total Protein, True Albumin, Total Globulin, Alpha Globulin, Beta Globulin, and Gamma Globulin in 1.0 ml. of Serum, Am. J. Clin. Path. **18**:723, 1948.

cardiograms, liver-function tests, bone marrow studies, and roentgenograms of involved joints were obtained in most instances, with results as listed below where significant.

Sedimentation rates were elevated in all patients. All leucocyte counts were within normal limits (except in Case 9 as noted). Other abnormalities were noted in the case reports only if significant. Those patients in whom laboratory tests suggested liver dysfunction gave no other evidence of liver disease. These abnormal results on liver-function tests were believed to reflect changes in serum globulin and liver damage as part of the generalized disease.

Patients were selected for the study because of the presence of significant lymph node enlargement. In addition, we included two (Cases 4 and 7) with only slightly enlarged lymph nodes. At the time of writing, periods up to two years have elapsed since the biopsies were performed.

The histologic specimens were stained with hematoxylin and eosin. In several instances serial sections were examined.

REPORT OF CASES AND PATHOLOGIC FINDINGS

CASE 1.—*History.*—A 42-year-old white woman had rheumatoid arthritis of two and one-half years' duration. Axillary lymph node enlargement was observed during the summer of 1949. Physical examination (November, 1949) revealed posterior cervical, left supraclavicular, bilateral axillary, and inguinal nodes of 1.5 to 3 cm. in diameter. These were nontender and freely movable. There was no splenomegaly. The usual articular lesions of rheumatoid arthritis involved knees, elbows, wrists, and hands.

Laboratory tests revealed mild hypochromic anemia (erythrocytes, 4,200,000; hemoglobin concentration, 10.0 gm. per 100 cc.). Total protein was 8.1 gm. (albumin, 3.0 gm.; globulin, 5.1 gm.; gamma globulin, 2.45 gm.); thymol turbidity, 7.2 units, and cephalin flocculation, 2+ (after 48 hours).

Because of an initial histologic diagnosis of giant follicular hyperplasia, x-ray therapy was given to the involved nodes, with a resultant slight diminution in size but without improvement of the arthritis. Homologous serum hepatitis appeared in April, 1950, with partial relief of articular symptoms.

The total period of observation was one and one-half years.

Pathologic Changes in Axillary Lymph Node (Fig. 1).—The architectural pattern was fairly well preserved. There was marked follicular hyperplasia throughout with occasional fusion of lymph follicles (Fig. 2). Follicles varied in size. The marginal sinuses were compressed; some sinuses were filled with lymphoid cells. Much activity was noted in the germinal centers, with mitotic figures and some variation in size, shape, and staining quality of nuclei. Many cells showed vesicular nuclei with prominent nucleoli. Others showed dark-staining nuclei with eosinophilic cytoplasm. There was an increased number of lymphocytes within the germinal centers with cord-like arrangement. There was thickening but no lymphocytic infiltration of the capsule. Reticuloendothelial activity in the interfollicular tissue was minimal.

Because of marked follicular hyperplasia and follicular fusion, the diagnosis was considered initially to be giant follicular hyperplasia or early lymphosarcoma. After further review of our material, this specimen was considered to show marked reactive hyperplasia in rheumatoid arthritis.

CASE 2.—*History.*—A 25-year-old white woman complained of malaise, night sweats, weight loss, and generalized joint pains of seven weeks' duration. Four years previously this patient had suffered a bout of polyarthritis of several months' duration. Physical examination (October, 1950) revealed bilateral 1.5-cm. lymph nodes in axillary, epitrochlear, and inguinal areas. Enlarged lymph nodes were also noted along the inner aspect of the right arm. There was no splenomegaly. Small cystic swellings were present over the dorsa of the hands. There was symmetrical swelling with tenderness of knees, ankle, hands, wrists, and elbows.

Laboratory studies showed 3+ cephalin flocculation (after 48 hours); 10% retention of sulfobromophthalein (bromsulphalein®) sodium after 45 minutes, and total protein of 6.8 gm. (albumin, 2.8 gm.; globulin, 4.0 gm.).

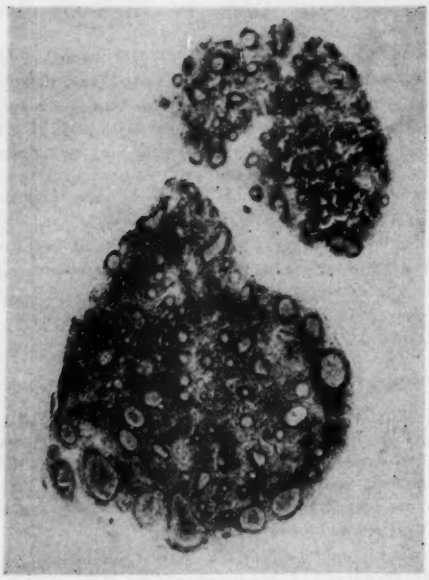

Fig. 1 (Case 1).—Hand-lens view of follicular hyperplasia of lymph node. Note marked increase of lymph follicles throughout lymph node with variability in size and shape and occasional fusion of follicles (Table 4).

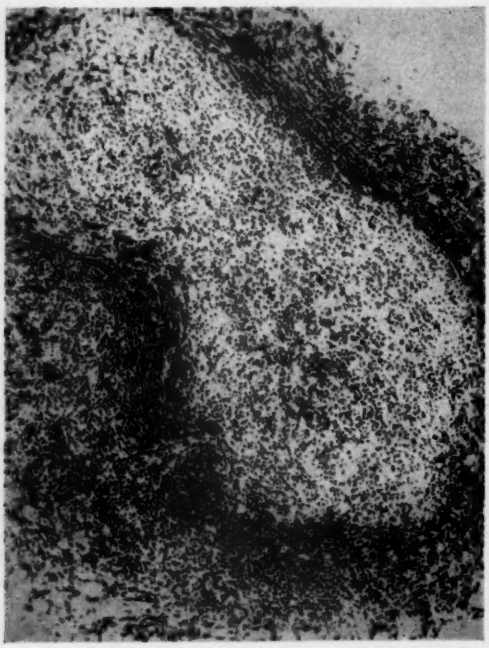

Fig. 2 (Case 1).—High-power view of follicular fusion. Note merging of two follicles into one large follicular structure; × 100.

Since the lymph node biopsy specimen initially was interpreted as showing possible giant follicular hyperplasia, the patient was given x-ray therapy to the enlarged lymph nodes. There was some shrinkage of the nodes but no improvement of the articular symptoms. Later this patient responded well to cortisone therapy. After six months of treatment with cortisone, the lymph nodes were only slightly enlarged.

The total period of observation was nine months.

Pathologic Changes in Epitrochlear and Axillary Lymph Nodes.—The architectural pattern was well maintained. The capsule was thin. A few lymphocytes were seen in the perinodal tissue. Relatively few follicles were present, and these were considerably larger than normal in size and irregular in shape. There was evidence of minimal "cracking" of the follicular edges, though there was no breaking-through or confluence. Germinal centers were relatively active, but few mitotic figures were noted. Adjacent to the hilus in the pulp were markedly dilated lymph sinuses containing lymphocytes, polymorphonuclear cells, eosinophiles, and plasma

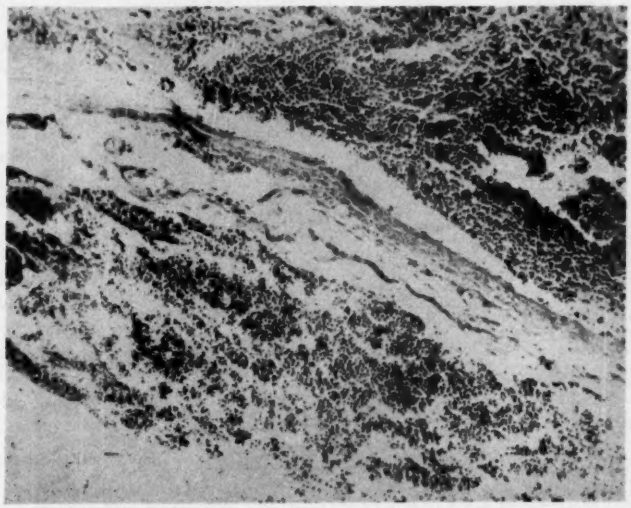

Fig. 3 (Case 3).—Invasion of pericapsular tissue with lymphocytes; × 100.

and histiocytic cells. Lymphocytes in the hilar region were loosely arranged. At the periphery of the follicles lymphoid cells were not compressed.

Because of some suggestive features ("cracking" and many very large follicles), this condition was initially interpreted as early giant follicular hyperplasia. Further review and comparison with the rest of our biopsy sections clearly indicated this to be reactive hyperplasia.

CASE 3.—*History.*—A 26-year-old Negro man stated that he had recurrent episodes of inflammation of large and small joints for one and a half years. He had been treated for arthritis since that time. Sizable lymph node enlargement was present since onset of the patient's illness, and three previous lymph node biopsies done at another hospital had been reported as showing nonspecific lymphadenitis.

Physical examination (September, 1950) revealed tenderness and swelling of all joints with an effusion of the left knee. There was characteristic spindling of the fingers. Nontender lymph nodes measuring 1 to 3 cm. were present in the axillae and in the cervical, epitrochlear, and inguinal areas. There was no splenomegaly.

Laboratory studies revealed normochromic, normocytic anemia (erythrocytes, 2,800,000; hemoglobin concentration, 8.1 gm.) and total protein of 6.9 gm. (albumin, 2.5 gm.; globulin, 4.4 gm.); bone marrow biopsy revealed an increase of plasma cells. Roentgenograms showed osteoporosis of hands and wrists, with soft tissue swelling. The joint space was maintained.

Treatment with cortisone resulted in some degree of shrinkage of the enlarged lymph nodes, and a marked improvement of the joint symptoms was noted.

The total period of observation was nine months.

Pathologic Changes in Epitrochlear Lymph Node (After Cortisone Therapy).—The capsule was normal, but the adjacent fat tissue contained a small number of lymphocytes (Fig. 3). Marginal sinuses were compressed and contained many small lymphocytes intermingled with a few polymorphonuclear leucocytes. The follicles were numerous and larger than normal, some of them fusing by confluence and leaving large germinal centers. These centers showed moderate activity. Mitotic figures were not extremely numerous. The adjacent lymphocytes of the pulp were somewhat compressed. Occasional polymorphonuclear leucocytes and some edema-like material were noted in the pulp.

This lymph node clearly revealed marked reactive follicular hyperplasia but presented at least one of the features associated with giant follicular hyperplasia, follicular fusion.

CASE 4.—*History.*—A 46-year-old white woman had typical rheumatoid arthritis of 10 years' duration. In addition, bronchiectasis had been diagnosed by iodized oil (lipiodol®) studies.

Physical examination (July, 1949) revealed characteristic fusiform enlargement of the fingers of both hands and involvement of wrists and knees. There was marked bilateral axillary lymphadenopathy, with nodes of 2-cm. diameter. No splenomegaly was noted.

Laboratory studies disclosed normochromic, normocytic anemia (erythocytes, 3,600,000; hemoglobin concentration, 11.1 gm.); total protein of 8.6 gm. (albumin, 3.4 gm.; globulin, 5.2 gm.; gamma globulin, 2.25 gm.); 4+ cephalin flocculation (after 48 hours), and thymol turbidity of 4.2 units.

Marked progression of the arthritis developed, and the patient was lost from observation.

Pathologic Changes in Axillary Lymph Node.—There were many small and well-defined follicles. The capsule was thin. There was moderate activity of the germinal centers, but mitotic figures were sparse. The pulp showed no changes.

This was an instance of reactive follicular hyperplasia with no misleading features.

CASE 5.—*History.*—A 39-year-old Negro woman had migratory and recurrent inflammation of large and small joints eight months prior to admission. She discovered a painful right supraclavicular lymph node four months later. Physical examination on admission (April, 1950) revealed tender and swollen wrists and ankles. Shoulder motion was painful bilaterally. The liver was palpable 2 cm. below the costal margin. There was no splenomegaly. Tender axillary and supraclavicular lymph nodes were palpable. An enlarged lymph node was noted at the medial surface of the right mid-arm.

Laboratory studies showed total protein of 8.2 gm. (albumin, 3.8 gm.; globulin, 4.4 gm.); small T waves were noted on the electrocardiogram.

X-ray therapy resulted in complete disappearance of the enlarged lymph nodes. There was no improvement of the arthritis. This patient later had some relief from treatment with gold salts.

The total period of observation was one year.

Pathologic Changes in Supraclavicular Lymph Nodes.—The architectural pattern was preserved. The capsule was slightly thickened, and lymphocytes were noted in the pericapsular fat tissue. The sinusoids were somewhat compressed. Follicles were well demarcated and larger than normal (Fig. 4). There was marked activity in the germinal centers, and mitotic figures were numerous. The adjacent pulp was compressed, and many thin cords consisting of

rows of lymphocytes were seen adjacent to the follicles. The pulp contained an increased number of histiocytic cells. The cyptoplasm of several macrophages contained granular foreign material. Foci of edema were noted in the pulp, and there was an increase in connective tissue.

This patient with typical rheumatoid arthritis had painful lymph nodes and an enlarged lymph node at an unusual site (mid-arm). The lymph node biopsy specimens showed reactive follicular hyperplasia with some misleading features which led to x-ray therapy for a histologic diagnosis of giant follicular hyperplasia.

CASE 6.—*History.*—A 20-year-old white girl had complained of pain and swelling of large and small joints for two years prior to admission. On admission (September, 1949) there was characteristic fusiform enlargement of her fingers, cystic swellings of the dorsa of both hands, and painful swollen ankles. There was nontender bilateral axillary and inguinal lymph node enlargement of 1.5-cm. diameter.

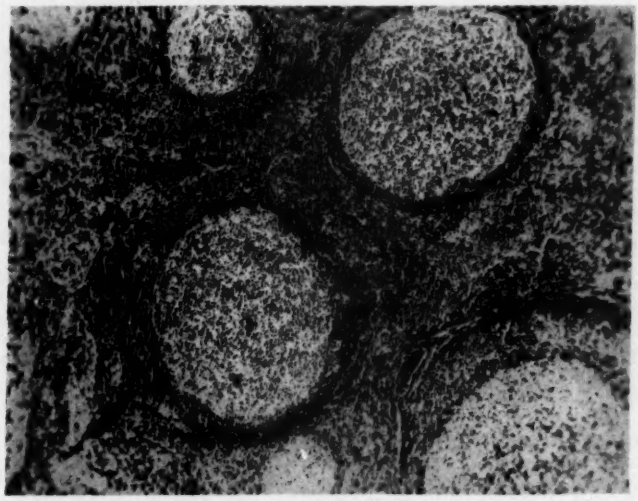

Fig. 4 (Case 5).—Reactive hyperplasia with typically enlarged follicles; × 70.

Laboratory results were not remarkable. Total protein was 8.1 gm. (albumin, 4.0 gm.; globulin, 4.1 gm.). The patient was given radiation therapy to the involved lymph nodes, with little improvement of her arthritis. She was lost from observation.

Pathologic Changes in Axillary Lymph Node.—The architectural pattern was somewhat obscured, but individual lymph follicles were recognized easily at the periphery of the node. The capsule of the lymph node showed occasional infiltration with lymphocytic cells. Within the center of the node the follicles were larger than normal and were surrounded by compressed lymphocytes arranged in thin cords. There was moderate activity within the germinal centers, and a few mitotic figures were observed. Here and there fibroblastic proliferation and newly formed connective tissue were noted.

This lymph node was an example of marked chronic lymphoid hyperplasia. Several unusual features, such as lymphocytic infiltration of the capsule and the large follicles, led one observer initially to advise x-ray therapy.

CASE 7.—*History.*—A 51-year-old Negro woman had polyarthritis of 24 years' duration. On admission there was involvement of all large and small joints with the typical lesions of

rheumatoid arthritis. An effusion of the left knee was also noted. Bilateral nontender 1-cm. cervical and axillary lymph nodes were palpated.

Laboratory studies disclosed mild hypochromic anemia (hemoglobin concentration, 11.9 gm.; erythrocytes, 4,200,000) and total protein of 7.9 gm. (albumin, 3.7 gm.; globulin, 4.2 gm.). Gold therapy was started, and the patient was discharged after a cervical node biopsy.

The total period of observation was three months.

Pathologic Changes in Cervical Lymph Node.—The capsule was thin. The marginal sinuses were open. A few follicles with only moderate cellular activity were seen. The pulp showed an increase in number of reticulum cells. A few plasma cells were also seen.

This clearly was an example of chronic lymphoid hyperplasia and did not lead to discussion.

CASE 8.—*History.*—A 16-year-old boy exhibited polyarthritis in the summer of 1949, associated with weight loss, malaise, anemia, and generalized lymph node enlargement. A lymph node

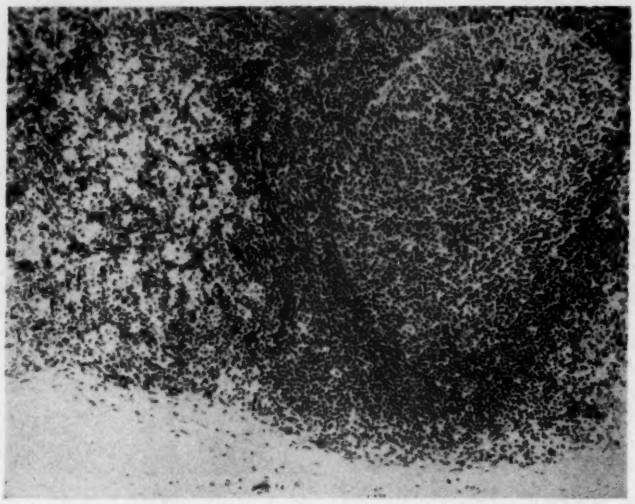

Fig. 5 (Case 8).—Follicular hyperplasia adjacent to marked reticuloendothelial activity in pulp. Note presence of the important histologic patterns in rheumatoid arthritis in same microscopic field; × 100.

biopsy performed elsewhere suggested features of Hodgkin's disease to some observers. The patient was treated with nitrogen mustard (methyl-*bis* [β-chloroethyl] amine hydrochloride) and later with x-irradiation. There was good response in his general well-being to the first course of nitrogen mustard, as well as improvement of the arthritis. Progressive deterioration of systemic symptoms and flare-up of polyarthritis occurred in the fall of 1950.

Physical examination (October, 1950) revealed a chronically ill boy with shotty axillary, epitrochlear, and inguinal lymph nodes of 1-cm. diameter. The liver was palpable 2 cm. below the costal margin. The splenic tip was palpable on deep inspiration. Knees, wrists, and hands were involved by the lesions of rheumatoid arthritis. Early contraction deformities were noted at both elbows.

Laboratory investigation revealed normochromic, normocytic anemia (erythrocytes, 3,500,000; hemoglobin concentration, 10.4 gm.) and total protein of 8.8 gm. (albumin, 2.9 gm.; globulin, 5.9 gm.). The electrocardiogram showed inverted T waves. Roentgenograms showed osteoporosis.

Septicemia and signs of myocarditis developed with corticotropin (ACTH) therapy. He recovered after discontinuance of corticotropin administration.

The total period of observation was one and one-half years.

Pathologic Changes in Axillary Lymph Nodes (Summer, 1949).—The capsule was slightly thickened and infiltrated by a few lymphocytes. The sinuses were markedly compressed. Follicles with hyperplastic germinal centers were abundant. Fusion of germinal centers was occasionally noted. The lymphoid cells adjacent to the follicles were markedly compressed and arranged in cord-like fashion. There was marked proliferation of reticulum cells, some of which contained phagocytized material. Most reticuloendothelial cells were intimately intermingled with lymphocytes. There were a few mitotic figures among the reticulum cells, and here and there variation in size and shape was noted.

An epitrochlear biopsy specimen examined in the fall of 1950 was interpreted as less "malignant." There were small follicles; however, hyperplastic germinal centers with many mitotic figures and marked proliferation of reticulum cells in the pulp (Fig. 5) continued to be present.

Because of the presence of large atypical reticuloendothelial cells, the first biopsy specimen suggested Hodgkin's disease to some observers. The patient was given nitrogen mustard with fairly good result. This is interesting in view of the reported successful treatment of rheumatoid arthritis with nitrogen mustard.[14] Our pathologist suggested the possibility of an early lymphosarcoma. The second biopsy specimen clearly showed evidence of nonspecific chronic lymphadenitis. In retrospect, this appears to be a case of rheumatoid arthritis resembling Still's disease, though a malignant lymphoma cannot be completely ruled out, owing to the short length of observation.

CASE 9.—*History.*—A 25-year-old Negro woman had suffered from arthritis with involvement of hands, shoulders, hips, and dorsum of right foot for several years. For several months before admission there were malaise and marked weight loss.

On physical examination (April, 1950) fusiform enlargement of the fingers and tenderness on motion of hips and shoulders were noted. Lymph nodes of 2.5-cm. diameter were present in the axillary, epitrochlear, cervical, and inguinal areas. The liver was palpable 2 cm. and the spleen 1 cm. below the costal margin.

Laboratory studies showed leucopenia (4,300 cells) with atypical lymphocytes. No anemia was present. There was marked increase of plasma cells in the bone marrow (15%). A heterophil antibody test revealed a rising titer up to 1:160. The Kahn reaction was doubtful (biologically false-positive). The Bence Jones test on urine gave a negative result. Total protein was 10.3 gm. (albumin, 2.1 gm.; globulin, 8.2 gm.; gamma globulin, 4.7 gm.); thymol turbidity, 6.0 units, and cephalin flocculation, 3+ (after 48 hours).

A cervical lymph node biopsy was performed during the course of the infectious mononucleosis. The patient was discharged but was readmitted four months later with systemic symptoms including meningismus. Pyodermal lesions were present, and hepatomegaly persisted. An axillary lymph node biopsy was performed. Because of some features suggesting lymphoma, x-ray therapy was given to the involved nodes, with some improvement of articular symptoms. She was admitted again after six months because of pyoderma. Hyperglobulinemia and marked increase of plasma cells in the bone marrow persisted. The L-E test was negative. Skeletal survey was negative for multiple myeloma. A Frei reaction was negative. A cervical lymph node biopsy was performed during this admission.

Pathologic Changes in Lymph Nodes.—Cervical Lymph Node (April, 1950): Follicles were slightly increased, relatively small, and well circumscribed. There was marked activity within the germinal centers, and mitotic figures were in abundance. Marginal sinuses were slightly compressed. There was some edema in the adjacent fat tissue. Occasional lymphoid pleomorphism in the pulp was noted.

14. Jiménez Díaz, C.; Lopez García, E.; Merchante, A., and Perianes, J.: Treatment of Rheumatoid Arthritis with Nitrogen Mustard, J. A. M. A. **147**:1418, 1951.

Axillary Lymph Node (August, 1950): The architectural pattern was somewhat obscured, but the follicles were easily recognized. The sinuses were compressed, and there was invasion of the adjacent fat and connective tissue septa by small lymphocytes. Occasionally there was fusion of two follicles. There were many mitotic figures within the germinal centers. Macrophages were not numerous. Within the follicles numerous densely packed large or small lymphocytes were seen. There was moderate increase in newly formed connective tissue, particularly noticeable in perivascular regions.

Cervical Lymph Node (February, 1951): This lymph node showed features similar to those seen in the first biopsy specimen.

The patient presented several unusual features but was included in this series since no disease other than rheumatoid arthritis could be found to account for her arthritis. Interpretation of the first biopsy specimen was complicated by the

TABLE 3.—*Summary of Essential Histologic Features of Lymph Nodes Examined**

Case No.	Age; Sex	Follicular Hyperplasia	Fusion of Follicles	Lymphatic Sinuses	R-E Activity in Interfollicular Tissue	Capsular Lymphocytic Infiltration	Connective Tissue Proliferation	Miscellaneous
1	42 F	4+	Present	Compressed	Minimal	...	Capsular thickening	....
2	28 F	1+	.....	Widely open	Minimal	1+	.....	Polymorphonuclear cells, plasma cells, "cracking"
3	26 M	3+	Present	Compressed	Minimal	2+	.....	Polymorphonuclear cells, edema
4	46 F	2+	.....	Open	Minimal	...	.....	....
5	30 F	2+	.....	Slightly compressed	Increased with phagocytosis	2+	Capsular thickening newly formed connective tissue	Edema
6	20 F	2+	.....	Normal to slightly compressed	Minimal	2+	Newly formed connective tissue	....
7	51 F	...	.....	Open	Increased	...	.....	Plasma cells
8	16 M	3+	Present	Compressed	Markedly increased with phagocytosis	2+	Capsular thickening	Polymorphonuclear cells
9	25 F	1+	Present	Slightly compressed	Minimal	3+	Newly formed connective tissue	Edema

* Extent of follicular hyperplasia and of lymphocytic infiltrations of the capsule arbitrarily graded 1 to 4+. R-E means reticuloendothelial.

presence of infectious mononucleosis and that of the second and third by the coexisting pyoderma. The first biopsy specimen showed reactive hyperplasia. The second biopsy raised the possibility of an early nonspecified lymphoma, for which this patient was treated with x-ray therapy. The patient's pyodermal lesions definitely contributed to the persistence of her adenopathy. However, there were no skin lesions when she was first seen.

COMMENT

Table 3 summarizes the important histologic features of the lymph nodes examined.

Commonly accepted criteria for the differentiation of reactive hyperplasia from true giant follicular hyperplasia are shown in Table 4 (modified after Heck and

Baggenstoss [15]). With the use of these criteria, it became clear that in none of our cases could the follicular hyperplasia unequivocally have been called true giant follicular hyperplasia. On the other hand, it is also shown that several of the criteria sometimes considered to be pathognomonic for giant follicular hyperplasia, such as giant follicles, fusion of follicles, tendency of follicles to be separated from surrounding tissue ("cracking"), and capsular infiltration by lymphocytes, may be encountered in the lymphadenopathy associated with rheumatoid arthritis.

Our material provides much evidence of the systemic nature of rheumatoid arthritis. Findings such as hyperglobulinemia, plasmacytosis in the bone marrow, positive results on liver-function tests, hepatomegaly, normochromic or hypochromic anemia, and various electrocardiographic abnormalities point to the generalized character of this disease in our cases. Our findings indicate that such patients exhibit

TABLE 4.—*Histologic Criteria for Differentiation of Giant Follicular Lymphoblastoma from Reactive (Toxic, Inflammatory) Hyperplasia of Lymph Nodes**

Criteria	Reactive Hyperplasia	Giant Follicular Hyperplasia
Location of lymph follicles	Cortex arranged in concentric rows	Throughout lymph node including medulla
Number of follicles	Few	Many
Size of follicles	Relatively small; may vary in size	Large ("giant")
Fusion of follicles	Absent	Frequently present
Interfollicular tissue	Scattered cells	Cells densely packed
Lymph sinuses	Open and often dilated	Narrow, compressed, not dilated
Proliferation of reticuloendothelial cells	Marked	Slight
Phagocytosis by reticuloendothelial cells	Frequent	Absent
Reticulum	Loose	Condensed
Miscellaneous	"Starry-sky" appearance within follicles	Tendency of follicles to be separated from surrounding tissue ("cracking") Pericapsular infiltration with lymphocytes

* Modified from Baggenstoss and Heck.[15]

more significant lymphadenopathy than those with low-grade, mild rheumatoid arthritis.

Follicular hyperplasia resembling that seen in giant follicular hyperplasia (Brill-Symmers disease) is a not infrequent pattern in lymph nodes of patients with rheumatoid arthritis. Others have reported similar observations. Bauer [2d] comments on two patients with rheumatoid arthritis who, at the onset of their illness, had generalized lymphadenopathy with minimal articular symptoms. For both patients a diagnosis of giant follicular lymphoblastoma was made by "a very competent pathologist." Further clinical observation pointed against such an interpretation. Graham [16] reported two instances in which a diagnosis of giant follicular hyperplasia was made, but later developments challenged the validity of such a diagnosis.

15. Baggenstoss, A. H., and Heck, F. J.: Follicular Lymphoblastoma (Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen), Am. J. M. Sc. **200**:17, 1940.

16. Graham, W., in discussion on Motulsky, A. G.; Weinberg, S. L.; Saphir, O., and Rosenberg, E.: Significance of Giant Follicular Hyperplasia in the Lymphadenopathy of Rheumatoid Arthritis, abstracted, Ann. Rheumat. Dis. **10**:486, 1951.

American literature is scanty on pathology of lymph nodes in rheumatoid arthritis. Proliferation of reticuloendothelial cells in sinuses of lymph nodes was observed in 7 of 14 cases studied at necropsy by Baggenstoss and Rosenberg.[17] Reticuloendothelial proliferation in follicles was seen in one case; suppurative lymphadenitis, in two cases; degeneration of secondary centers of lymph follicles, in two cases, and amyloid deposits, in the remaining two cases. In these patients striking lymphadenopathy was not observed during life. No mention of follicular hyperplasia was made in this report.

Analysis of lymph node biopsy specimens from eight patients with rheumatoid arthritis was reported from France by Poursines and Rochu.[4b] These authors stressed (1) proliferation and hyperplasia of reticulum cells and (2) "fibroblastic metaplasia" of reticulum cells with resulting newly formed connective tissue. They mentioned the presence of large multinucleated reticuloendothelial cells closely resembling Sternberg-Reed elements as giving difficulties in the differentiation from Hodgkin's disease. Lymphoid aplasia with marked sclerosis of the lymph nodes ("lymph node cirrhosis") was mentioned as accompanying rheumatoid arthritis of long standing. Follicular hyperplasia was not commented on. These authors concluded that, since lymph node lesions in rheumatoid arthritis and Still's disease are similar, these two diseases are fundamentally identical. Earlier continental writers [18] on the histology of lymph nodes in rheumatoid arthritis were said to have come to essentially similar conclusions concerning lymph node pathology of rheumatoid arthritis and its relation to Still's disease. These workers noted occasional instances of follicular hyperplasia associated with the more usual reticuloendothelial proliferation.

Robb-Smith,[19] in a general review of lymph node biopsy interpretation, stated that follicular hyperplasia is the usual feature of lymph node histology in rheumatoid arthritis. Collins [20] briefly discussed the pathology of the lymph nodes in rheumatoid arthritis. He merely described simple reactive hyperplasia of sinus reticulum and of follicles, sinus catarrh, and a variable degree of fibrosis.

Parkes Weber [12c] reported one case of rheumatoid arthritis with painless adenopathy and marked follicular hyperplasia on biopsy. This writer published an illustration of a biopsy section and warned that such histologic findings should not be confused with early stages of follicular lymphoblastoma of neoplastic origin. Two cases of rheumatoid arthritis with histologic features resembling giant follicular lymphoblastoma were reported from Spain by Jiménez-Díaz and co-workers.[4c] The pathologic findings in one case were said to be indistinguishable from those of Brill-Symmers disease, including enormous follicular hyperplasia associated with complete transformation of the nodal architecture and occlusion of lymph sinuses. In an extensive study of a case of rheumatoid arthritis with marked generalized lymphadenopathy, Rotes Querol and Ciscar Rius [8] noted histologic lymph node lesions identical with those seen in classic Brill-Symmers disease.

17. Baggenstoss, A. H., and Rosenberg, E. F.: Visceral Lesions Associated with Chronic Infectious (Rheumatoid) Arthritis, Arch. Path. **35**:503, 1943.

18. Delarue (1934), and Giordano (1934), cited by Poursines and Rochu.[4b]

19. Robb-Smith, A. H. T.: The Lymph Node Biopsy, in Recent Advances in Clinical Pathology, edited by S. C. Dyke, Philadelphia, The Blakiston Company, 1947.

20. Collins, D. H.: The Pathology of Articular and Spinal Diseases, Baltimore, Williams & Wilkins Company, 1949.

In a personal communication, Baggenstoss [21] stated that differentiation of giant follicular hyperplasia from histologic features of lymph nodes in rheumatoid arthritis is made by the appearance of the lymphatic sinuses. In rheumatoid arthritis the sinuses are usually dilated and reveal extensive proliferation of the lining cells, with frequent phagocytosis of hemosiderin. In contrast, massive growth of the follicles with compression of lymphatic sinuses is characteristic of giant follicular hyperplasia.

In a recent syllabus of tumors [22] a picture of a lymph node from a patient with "hypertrophic arthritis" is shown as an example of giant follicular lymphoblastoma. This very likely could represent another instance of severe follicular hyperplasia.

In a fundamental contribution to the problem of lymph node lesions in rheumatoid arthritis, Farreras Valenti [4a] pointed out that lymph nodes in rheumatoid arthritis may be the seat of three fundamentally different reactions:

1. A Proliferative-Inflammatory Type: This is seen in Still-Chauffard-Felty disease and in some instances of classic rheumatoid arthritis. It is manifested by

TABLE 5.—*Previously Reported Cases of Rheumatoid Arthritis with Lymph Node Lesions Similar to Giant Follicular Lymphoblastoma*

Parkes Weber (1944) [12c]	Marked follicular hyperplasia; general proliferative activity
Jiménez-Díaz and others (1946) [4c]	Case 1: Intense follicular hyperplasia with large germinal centers; sinuses blocked by proliferation of reticuloendothelial cell
	Case 2: Enormous follicular hyperplasia; obliteration of sinuses; transformation of normal architecture
Rotes Querol and Ciscar Rius (1948) [8]	Marked increase in number and size of lymph follicles in cortex and medulla with few reticular and sinusoidal elements remaining
Bauer (1950) [9d]	2 cases with diagnosis of giant follicular lymphoma by "very competent pathologist"
Graham (1951) [14]	2 cases with diagnosis of giant follicular lymphoma

diffuse hyperplasia of all reticuloendothelial elements and dilated lymph sinuses filled with plasma cells, histiocytes, polymorphonuclear cells, and eosinophiles.

2. A Hyperplastic-Neoplastic Type: Here one finds marked follicular hyperplasia with fusion of follicles and compression of interfollicular tissue. This lesion, which we observed and others have also described in a few cases of rheumatoid arthritis, causes difficulty in differential diagnosis from giant follicular lymphoblastoma.

3. A Proliferative-Granulomatous Type: In this variety of lymph node reaction, the histologic picture is said to be that of sarcoidosis. Three cases of coexisting sarcoidosis and rheumatoid arthritis [23] were cited from the literature. Since sarcoidosis not infrequently may be associated with polyarthritis resembling rheumatic fever or rheumatoid arthritis,[24] the contention that lymph nodes in rheumatoid arthritis may show lesions of sarcoidosis must be rejected.

21. Baggenstoss, A. H.: Personal communication to the authors.

22. Mulligan, R. M.: Syllabus of Human Neoplasms, Philadelphia, Lea & Febiger, 1951.

23. Jiménez Díaz and others.[4c] Castellanos, A., and Galan, E.: Sarcoidosis: Report of a Case in a Child Simulating Still's Disease, Am. J. Dis. Child. **71**:513, 1946. Zweifel, E.: Gleichzeitiges Vorkommen eines Boeckschen Sarcoid mit einer primären chronischen Polyarthritis, Helvet. paediat. acta **1**:475, 1945-1946.

24. Myers, G. B.; Gottlieb, A. M.; Mattmann, P. E.; Eckley, G. M., and Chason, J. L.: Joint and Skeletal Muscle Manifestations in Sarcoidosis, Am. J. Med. **12**:159, 1952.

Farreras Valentí concluded that the manner in which lymph nodes can react is limited. Depending upon constitutional predisposition and acquired "allergic" factors, lymph nodes, therefore, may react to the unknown agent of rheumatoid arthritis in only one of the three outlined patterns.

It may be argued that arthritis associated with preneoplastic or neoplastic lymph node lesions represents a systemic symptom of an underlying lymphomatous disease. However, we found no mention of arthritis as a symptom of giant follicular hyperplasia or the other lymphomas in several papers on the subject [25] (Table 2). Our own studies of such patients have also failed to disclose any articular symptoms. The only disease which may give rise to differential diagnostic difficulties is acute leukemia presenting as acute polyarthritis due to periosteal infiltrations.[26]

A relationship of lymphomas to rheumatoid arthritis might be postulated if there were an increased incidence of malignant lymphoma among patients suffering from rheumatoid arthritis. However, no investigator of the clinical features of either rheumatoid arthritis [1] or malignant lymphoma [25e] reports such a coincidence, nor have we noticed it in our clinical experience.

The coincidence of rheumatoid arthritis and lymph node lesions simulating lymphoma appears to be higher than chance. Follicular hyperplasia exists in various degrees of severity with rheumatoid arthritis, from very mild to extremely marked hyperplasia coupled in some instances with marked reticuloendothelial hyperactivity in the same lymph node (Case 8, Fig. 5). This suggests that follicular hyperplasia is a frequent histologic pattern by which lymph nodes react to rheumatoid arthritis. This conclusion is strengthened by the reported disappearance of enlarged lymph nodes when rheumatoid arthritis spontaneously regresses.[27]

Counterparts of follicular hyperplasia of lymph nodes may be found in the synovial membranes in rheumatoid arthritis. Here nodular collections of lymphocytes and reticuloendothelial cells with germinal centers similar to lymph node follicles are frequently found. Allison and Ghormley [28] claim that these lesions are specific for rheumatoid arthritis. Such follicle-like lesions in the synovial membranes may be of the same significance as the histologically similar lymph node lesions of follicular hyperplasia.

Since adrenocortical insufficiency usually is accompanied with lymphoid hyperplasia [29] and adrenocortical therapy is followed by lymphoid involution,[30] one may speculate on the relation of the adrenal gland to the follicular hyperplasia observed

25. (*a*) Footnote 11. (*b*) Cohen, S. E., and Bergstrom, V. W.: Giant Follicular Lymphoblastoma, Am. J. Clin. Path. **16**:22, 1946. (*c*) Gall, E. A.; Morrison, H. R., and Scott, A. T.: The Follicular Type of Malignant Lymphoma, Ann. Int. Med. **14**:2073, 1941. (*d*) Mayer, S., Jr., and Thomas, H. E., Jr.: Follicular Lymphoblastoma and a Related Form of Lymphosarcoma, Bull. Johns Hopkins Hosp. **64**:315, 1939. (*e*) Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease and Allied Disorders, New York, Oxford University Press, 1947 (Complete bibliography).

26. Bichel, J.: Arthralgic Leukemia in Children, Acta haemat. **1**:153, 1948.

27. Rotes Querol and Ciscar Rius.[8] Parkes Weber.[12c]

28. Allison, N., and Ghormley, R. K.: Diagnosis in Joint Disease, Baltimore, William Wood & Company, 1931.

29. Jaffe, H. L.: The Suprarenal Glands, Arch. Path. **3**:414, 1927.

30. Dougherty, T. F., and White, A.: An Evaluation of Alterations Produced in Lymphoid Tissue by Pituitary-Adrenal Cortical Secretion, J. Lab. & Clin. Med. **32**:584, 1947.

in rheumatoid arthritis. Cortisone therapy in several instances produced a definite reduction in size of the involved lymph nodes. A biopsy following cortisone therapy in Case 3, however, did not show any significant changes in total lymph node structure from that seen in other cases. The absence of any other stigmata of adrenocortical insufficiency in rheumatoid arthritis in general, and in our cases specifically, makes it highly unlikely that the follicular hyperplasia seen is a sign of adrenocortical insufficiency. It is well recognized that cortisone and corticotropin act as pharmacologic agents and not as substitution therapy in the suppression of the symptoms of rheumatoid arthritis. However, disturbances of steroid hormone metabolism, such as failure of physiologic progesterone conversion [31] and excretion of abnormal steroid hormones,[32] already have been demonstrated in this disease. We, therefore, cannot exclude the possibility that the lymphoid hyperplasia of rheumatoid arthritis may be mediated by a yet unknown mechanism of the adrenal cortex. Similar explanations have been invoked for the not infrequent lymphoid hyperplasia of hyperthyroidism [33] and myasthenia gravis. In that connection further studies on adrenal, thyroid, and thymus structure in rheumatoid arthritis will be welcome.

Recent, yet unconfirmed, reports on the treatment of rheumatoid arthritis with nitrogen mustard [14] raise the question whether the claimed results were produced by a corticotropin-like effect or by direct action on the lymphatic and reticuloendothelial system, which, as it has been shown, may be involved in rheumatoid arthritis. Certainly the role of these tissues in the pathogenesis of rheumatoid arthritis deserves further attention.

Every physician confronted with a patient who shows generalized lymph node enlargement associated with systemic symptoms and possible splenomegaly will suspect malignant lymphoma. An apparently confirmatory histologic diagnosis in the presence of such a clinical picture will make it difficult to withhold specific therapy. Thus, six of our patients received x-ray therapy, and one patient was given nitrogen mustard. Such therapy reduced enlarged lymph nodes in size but did not improve the underlying arthritis except in one patient (Case 8), who had been given nitrogen mustard elsewhere.

None of our patients have been followed long enough to allow a categorical statement that they do not have malignant lymphoma. It is our conclusion, however, that the lymph node lesions seen represent a clinical manifestation of the primary disease, rheumatoid arthritis. We feel, therefore, that if a patient with rheumatoid arthritis has lymph node lesions suggestive but not entirely typical of giant follicular hyperplasia or other lymphomas, x-ray therapy may be safely withheld, provided such a patient can be followed closely. Similarly any previous diagnosis of giant follicular lymphoblastoma in a patient with rheumatoid arthritis must be seriously questioned.

From the foregoing it seems clear that because of the spurious differentiation of the lymph nodes here described from giant follicular hyperplasia, which is a pre-

31. Sommerville, I. F.; Marrian, G. F.; Duthie, J. J. R., and Sinclair, R. J. G.: Abnormality in Steroid Metabolism Associated with Rheumatoid Arthritis, Lancet **1**:116, 1950.

32. Dobriner, K.: Adrenal Function and Steroid Excretion in Disease, in Symposium on Steroids in Experimental and Clinical Practice, edited by A. White, Philadelphia, The Blakiston Company, 1951, pp. 130-150.

33. Levy, R. C., and Levin, H. G.: Thyrotoxicosis Simulating Features of Lymphoma, Ann. Int. Med. **35**:1371, 1951.

cursor of malignant lymphoma, close cooperation among internist, radiotherapist, and pathologist is essential. If in some of the cases here presented the pathologist had been aware of the patient's total clinical picture, a correct diagnosis might have been arrived at and the poor prognosis and subsequent irradiation treatment might have been avoided.

SUMMARY

Significant generalized lymph node enlargement, not necessarily related to involved joints, may be found in 50 to 75% of cases of adult rheumatoid arthritis. Lymphatic system involvement is frequently observed in juvenile rheumatoid arthritis (Still's disease) and may be seen in Felty's syndrome.

Literature dealing with pathology and significance of lymph node enlargement in rheumatoid arthritis is reviewed. Nine patients with generalized rheumatoid arthritis were subjected to lymph node biopsy with the following findings:

1. Lymph nodes in rheumatoid arthritis showed a variable histopathologic reaction. Lesions observed were not uniform and not specific for rheumatoid arthritis.

2. The following histologic patterns were noted:

A. Follicular hyperplasia: This varied from obvious reactive hyperplasia with small follicles in the cortex of the lymph node to massive giant follicular hyperplasia throughout, with compression of interfollicular tissue and fusion of lymph follicles.

B. Invasion of Fat Tissue and Capsule: Lymphocytic infiltration was frequently noted around the fatty tissue of the lymph node capsule.

C. Reticuloendothelial Activity: This varied from minimal to marked reticuloendothelial proliferation, especially of the lymph sinuses, and was often associated with phagocytosis. Cells resembling Sternberg-Reed elements were seen.

D. Lymphatic Sinuses: Usually these were not completely compressed and when opened contained mononuclear elements of reticuloendothelial origin.

E. Connective Tissue Proliferation: Frequently this was evidenced by capsular thickening and formation of new connective tissue within the lymph node.

F. Polymorphonuclear Cells and Focal Edema: Many polymorphonuclear cells and areas of focal edema were seen in the more acute cases.

3. In some instances the histologic features noted may lead to confusion in diagnosis because of similarities to giant follicular lymphadenopathy (Brill-Symmers disease), lymphosarcoma, and Hodgkin's disease. Possible relations between these diseases and rheumatoid arthritis, as well as the role of the adrenal cortex, are discussed.

4. In spite of spurious similarities to malignant lymphomas, it is shown by study of our material and similar cases in the literature that the pathologic lesions encountered by us and others are characteristic of the lymphatic tissue reaction to rheumatoid arthritis and do not represent a separate disease process.

5. Close cooperation among internist, radiotherapist, and pathologist is essential in establishing a correct diagnosis in these instances.

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Progress in Internal Medicine

USE OF ANTIBIOTICS IN GASTROINTESTINAL DISEASES

A Review

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THE IMPORTANCE of antibiotics in medicine is reflected in the tremendous number of scientific papers published on the subject and the many new antibiotics described since penicillin became available. The clinically useful antibiotics at present are derived from the metabolic products of molds or filamentous fungi, from bacteria, and from the Actinomycetes.[1] The search for new antimicrobial

From the Department of Medicine, University of Chicago.

This paper was presented in part by Dr. Kirsner at the New England Postgraduate Assembly, Boston, November, 1951.

1. (*a*) Baron, A. L.: Handbook of Antibiotics, New York, Reinhold Publishing Corporation, 1950. (*b*) Benedict, R. G., and Langlyke, A. F.: Antibiotics, Ann. Rev. Microbiol. **1**:193, 1947. (*c*) Dowling, H. F.: The Present Status of Antibiotic Therapy, Antibiotics & Chemother. **1**:2, 1951. (*d*) Finland, M., and Wells, E. B.: The Antibiotics in Gastrointestinal Diseases, Rev. Gastroenterol. **17**:558, 1950. (*e*) Finland, M.: The Present Status of Antibiotics in Bacterial Infections, Bull. New York Acad. Med. **27**:199, 1951. (*f*) Florey, H. W.; Chain, E.; Heatley, N. G.; Jennings, M. A.; Sanders, A. G.; Abraham, E. P., and Florey, M. E.: Antibiotics, New York, Oxford University Press, 1949. Garrod, L. P.: (*g*) Chemotherapy: IV. The Newer Antibiotics, Brit. M. J. **2**:722, 1950; (*h*) The Reactions of Bacteria to Chemotherapeutic Agents, ibid. **1**:205, 1951. (*i*) Goldstein, A.: Antibacterial Chemotherapy, New England J. Med. **240**:180, 1949. (*j*) Grollman, A.: Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1951. (*k*) Irving, G. W., Jr., and Herrick, H. T.: Antibiotics, Brooklyn, Chemical Publishing Company, Inc., 1949. (*l*) Karel, L., and Roach, E. S.: A Dictionary of Antibiosis, New York, Columbia University Press, 1951. Keefer, C. S.: (*m*) Antibiotics: Yesterday, Today and Tomorrow, Ann. Int. Med. **33**:582, 1950; (*n*) Evaluation of Antibiotic Therapy, Postgrad. Med. **9**:101, 1951. (*o*) Kirby, W. M. M.: Recent Trends in Antibiotic Therapy, J. A. M. A. **144**:233, 1950. Kolmer, J. A.: (*p*) The Present Status of Antibiotic Therapy, Postgrad. Med. **4**:115, 1948; (*q*) Choice and Use of Chemotherapeutic Agents in General Practice, Pennsylvania M. J. **53**:506, 1950. (*r*) Long, P. H.; Chandler, C. A.; Bliss, E. A.; Bryer, M. S., and Schoenbach, E. B.: The Use of Antibiotics, J. A. M. A. **141**:315, 1949. (*s*) Long, P. H.; Schoenbach, E. B.; Bliss, E. A.; Bryer, M. S., and Chandler, C. A.: The Experimental and Clinical Use of Polymyxin, Chloromycetin and Aureomycin, California Med. **70**:157, 1949. (*t*) Long, P. H.; Bliss, E. A.; Schoenbach, E. B.; Chandler, C. A., and Bryer, M. S.: The Experimental Background and Clinical Use of Antibiotics, Lancet **1**:1139, 1950. Long, P. H.: (*u*) The Clinical Use of Antibiotics, M. Clin. North America **34**:307, 1950; (*v*) The Clinical Use of Antibiotics: Treatment of Infectious Processes, U. S. Armed Forces M. J. **1**:1273, 1950. (*w*) MacLeod, C.: Evaluation of Chemotherapeutic Agents, New York, Columbia University Press, 1949. (*x*) Miller, C. P.: New Problems in the Treatment of Infectious Diseases, Ann. Int. Med. **35**:673, 1951. (*y*) Most, H.: Recent Advances in the Therapy of the More Common Protozoan and Helminthic Infections of Man, Bull. New York Acad. Med. **25**:717, 1949. (*z*) Nelson, W. E.: Clinical Bases for Selection of Patients for Antimicrobial Therapy, J. A. M. A. **147**:1340, 1951. (*a'*) Pratt, R., and

(Footnote continued on next page)

agents has encompassed a wide variety of sources,[2] including human red blood cells, algae, toadstools, hops, the banana, the sweet potato, and even the onion, cabbage, turnip and horse-radish. Clinical studies on such new compounds as viomycin, fumagillin, picromycin,[3] and rhodomycin [4] are in progress. The many rapid developments in this field periodically require evaluation and review. The purpose of this paper is to survey briefly the current status of antibiotics in the treatment of gastrointestinal diseases.

PENICILLIN

Penicillin [5] is derived from the mold Penicillium notatum. The accepted preparation for clinical use is crystalline penicillin G; the standard method of administration is the parenteral. The oral use of penicillin has yielded satisfactory results in the treatment of systemic infections, but quantities three to five times larger

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Dufrenoy, J.: Mechanism of Antibiotic Actions and Trends in Antibiotic Chemotherapy, Texas Rep. Biol. & Med. **9**:76, 1951. (*b'*) Schoenbach, E. B.: The Newer Antibiotics: Polymyxin, Chloromycetin and Aureomycin, J. Mt. Sinai Hosp. **16**:71, 1949. (*c'*) Schrum, D., and Yow, E. M.: Choice of Antimicrobial Agents in Therapy of Infections, Texas J. Med. **47**:462, 1951. (*d'*) Shookhoff, H. B.: The Present Status of Antibiotics in the Treatment of Protozoan Diseases, Bull. New York Acad. Med. **27**:439, 1951. (*e'*) Spaulding, E. H., and Anderson, T. G.: Selection of Antimicrobial Agents by Laboratory Means, J. A. M. A. **147**:1336, 1951. (*f'*) Strax, S., and Wright, L. T.: Recent Advances in Antibiotic Therapy, New York J. Med. **49**:1797, 1949. (*g'*) Waksman, S. A.: Microbial Antagonisms and Antibiotic Substances, New York, Commonwealth Fund Division of Publications, 1945. (*h'*) Welch, H., and Lewis, C. N.: Antibiotic Therapy, Washington, D. C., The Arundel Press, Inc., 1951. (*i'*) Welch, H.; Reedy, R. J., and Wolfson, S. W.: A Comparison of the Effect of 9 Antibiotics on Experimental Typhoid Infections in Mice, J. Lab. & Clin. Med. **35**:663, 1950. (*j'*) Weinstein, L.: The Newer Antibiotics: A Brief Review of the Biological and Clinical Properties of Bacitracin, Polymyxin, Aureomycin, Chloromycetin and Neomycin, Ohio M. J. **46**:546, 1950.

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5. Blake, F. G.: The Therapeutic Indications of the Sulfonamides and Penicillin, J. A. M. A. **127**:517, 1945. Fleming, A.: Penicillin: Its Practical Applications, Ed. 2, St. Louis, C. V. Mosby Company, 1949. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, W. B. Saunders Company, 1945. Keefer, C. S., and Anderson, D. G.: Penicillin and Streptomycin in the Treatment of Infections, New York, Oxford University Press, 1950. Kolmer, J. A.: Penicillin Therapy, Ed. 2, New York, D. Appleton-Century Co., 1947.

than the parenteral dose are necessary because of poor absorption [6]; the oral route is less reliable and appears not to offer any striking advantage. Penicillin in vitro acts almost exclusively against aerobic and anaerobic Gram-positive organisms. Partial inhibition of certain Gram-negative intestinal bacteria has been described [7]; the resistant organisms produce penicillinase, the enzyme antagonizing the antimicrobial action of penicillin.[8]

Penicillin has been useful in the management of peritonitis in the dog and in the treatment of experimentally induced acute intestinal obstruction and strangulation.[9] Clinically, penicillin is of value in peritonitis caused by the Pneumococcus or Streptococcus and occurring after perforation of a peptic ulcer or of the appendix.[10] It is reportedly useful in Weil's disease (jaundice due to Leptospira icterohemorrhagiae) when administered early.[11] Penicillin is without beneficial effect in biliary dysentery, typhoid, and infections with Salmonella [12] and Escherichia coli. A chronic typhoid carrier apparently responded to treatment with penicillin and sulfamerazine after therapy with other sulfonamides, penicillin alone, and chloramphenicol had failed.[13] Favorable results have been noted occasionally in ulcerative colitis [14]; however, the recognizable fecal flora is not altered significantly. In our experience, penicillin is not consistently helpful in this disease. The combination of penicillin, sulfadiazine, and/or streptomycin may control secondary infections complicating ulcerative colitis.

Penicillin alone does not inhibit the growth of Endamoeba histolytica in vitro.[15] Penicillin and sulfonamides or streptomycin act synergistically in vitro and in

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15. Knoll, E. W., and Howell, K. M.: In Vitro Effect of Penicillin on Endamoeba Histolytica, Arch. Path. **42**:594, 1946.

animals against Gram-negative intestinal bacteria [16] and E. histolytica.[17] The combination constitutes useful adjunct therapy in peritonitis, amebic dysentery, amebic abscess of the liver,[18] and acute pancreatitis.[19] Penicillin given intravenously is excreted in high concentrations in the bile [20]; it has been used as an adjunct in the treatment of infections of the biliary tract.

Hypersensitivity to penicillin develops in approximately 2 to 5% of patients; the incidence is higher after local application and among persons with a history of allergy or previous contact with the antibiotic. The hypersensitivity is manifested by fever, skin eruptions, including urticaria and purpura, arthralgia, asthma, and, rarely, anaphylactic shock with death.[21] Peripheral neuritis has been described but seems to be unusual. Glossitis during penicillin therapy has been attributed to an alteration in vitamin B metabolism.[22] Bacterial strains resistant to penicillin, especially staphylococci, may emerge after prolonged or repeated treatment.

STREPTOMYCIN

Streptomycin is derived from a strain of the Actinomycetes, Streptomyces griseus.[23] Absorption is rapid after parenteral injection but poor after oral admin-

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istration; the latter route, consequently, is advantageous for local effect within the intestine. Streptomycin in vitro inhibits the growth of many Gram-negative intestinal bacilli, including Esch. coli, Eberthella typhosa (Salmonella typhi), Shigella, and Salmonella [24]; individual strains vary widely in susceptibility.[25]

Clinically,[26] streptomycin has been of value in Shigella infections, especially with organisms resistant to sulfonamides; in a typhoid-like infection attributed to the paracolon bacillus [27]; in bacteremia with Esch. coli, Salmonella choleraesuis, and Pseudomonas aeruginosa, and in gastroenteritis caused by Proteus organisms. Results in typhoid and most Salmonella infections have been variable and disappointing.[28] The drug is ineffective in amebic dysentery and amebic hepatitis.[29] Striking responses have been observed in several instances of acute ulcerative colitis [30]; streptomycin has not been consistently effective in the treatment of chronic ulcerative colitis.

Streptomycin is of particular value in the management of tuberculosis of the small and large intestine and the anorectal region. The antibiotic may be administered either parenterally or orally in doses of 1 or 2 gm. daily.[31] After prolonged treatment, tuberculous perianal sinuses or fistulas apparently may heal without surgical intervention. The development of resistant organisms, an exceedingly important disadvantage of streptomycin therapy, may be prevented or delayed by the simultaneous administration of paraaminosalicylic acid. The duration of improvement, frequency of relapse, and ultimate recovery from the intestinal tuberculosis obviously will be determined by the course of the associated pulmonary disease.

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Favorable results with streptomycin as an adjunct to surgical treatment have been described in occasional instances of acute cholecystitis, cholangitis, pylephlebitis, and liver abscesses with Gram-negative intestinal bacilli as the infecting organisms.

Streptomycin has been used as extensively in the preoperative and postoperative management of patients undergoing surgical procedures on the bowel.[32] Quantities of 0.5 gm. four times daily given by mouth or parenterally decrease the total bacterial count of the feces in man, chiefly by the inhibition of Esch. coli; streptococci, clostridia, yeasts, and the anaerobes persist. The suppressive effect occurs rapidly but is relatively brief. Bacterial counts usually increase after four to six days, despite continued administration of the antibiotic. Streptomycin does not "sterilize" the intestine. Lockwood and associates [32e] obtained exceedingly variable and unpredictable results. The simultaneous administration of glucuronolactone, 2 gm. daily by mouth, according to Pulaski,[32g] prolongs the suppression of coliform organisms to 14 days; disappointing results with this combination have been reported by others.[32h] Streptomycin has decreased the mortality from peritonitis caused by inflammatory and perforating lesions of the gastrointestinal tract, especially infections with a single Gram-negative organism or a mixed Gram-negative bacillary flora. The combination of streptomycin, penicillin, and/or sulfadiazine is more effective, since the flora usually includes both Gram-negative and Gram-positive bacteria. Bacterial resistance develops rapidly (within 24 hours) and involves a wide variety of organisms. Streptomycin-sensitive organisms rapidly return after discontinuance of treatment with the drug, but bacterial resistance may be prolonged. Streptomycin resistance apparently involves the inhibition of certain metabolic activities of nonproliferating cells of susceptible strains of bacteria; the problem has been studied extensively.[33]

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The incidence of undesirable effects with streptomycin is high.[34] Sensitization to streptomycin is manifested by fever, erythema and urticaria of the skin, and eosinophilia. The neurologic disturbances include irritation of the optic nerve (blurring of vision) and damage to the fifth and eighth cranial nerves (tinnitus, vertigo, and deafness); the vestibular dysfunction and deafness may be permanent. The literature contains reports of fatal anaphylactic shock, death of two patients with pulmonary tuberculosis who had stomatitis and dermatitis during streptomycin therapy,[35] hypoprothrombinemia, and fatal aplastic anemia.[36] The incidence of side-effects is related to the size of the daily dose and to the duration of treatment. However, the use of antihistaminic drugs or the reduction of the daily dose to 1 gm. has not entirely diminished or prevented the vestibular complication. Dihydrostreptomycin may cause similar undesirable effects if given in sufficiently large quantities [37]; in the presence of normal renal function neurotropic effects are considered unlikely if no more than 2 gm. is given daily for no longer than two weeks. In therapeutic amounts streptomycin does not impair hepatic or renal function.

AUREOMYCIN

Aureomycin [38] is derived from the liquor in which Streptomyces aureofaciens grows. It is readily absorbed after oral ingestion and may be taken with food or milk to decrease the tendency to digestive complaints; aluminum hydroxide inter-

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Development of Streptomycin Resistant Bacteria in the Stools of Patients Treated for Tuberculosis, J. Lab. & Clin. Med. **33**:1460, 1948. Hamburger, M., and Berman, J. R.: The Replacement of Streptomycin-Resistant Coliform Bacteria in the Stools by Streptomycin-Sensitive Variants During and Following the Cessation of Streptomycin Therapy, J. Clin. Invest. **29**:630, 1950. Demerec, M.: Patterns of Bacterial Resistance to Penicillin, Aureomycin and Streptomycin, ibid. **28**:891, 1949. Geiger, W. B.: Interference by Streptomycin with a Metabolic System of Escherichia Coli, Arch. Biochem. **15**:277, 1947. Henry, J.; Henry, R. J.; Housewright, R. D., and Berkman, S.: Studies on Streptomycin: III. Effect of Streptomycin on the Metabolism of Resting Bacteria and on Certain Purified Enzymes, J. Bact. **56**:527, 1948. Oginsky, E. L.; Smith, P. H., and Umbreit, W. W.: Action of Streptomycin: I. Nature of the Reaction Inhibited, ibid. **58**:747, 1949. Seligman, E., and Wasserman, M.: Induced Resistance to Streptomycin, J. Immunol. **57**:351, 1947. Umbreit, W. W.: Metabolic Action of Streptomycin, Ann. New York Acad. Sc. **53**:6, 1950. English, A. R., and McCoy, E.: Growth Comparisons of Streptomycin-Sensitive and Streptomycin-Resistant Micrococcus Pyogenes var. Aureus, J. Bact. **62**:19, 1951. Spingarn, C. L., and Edelman, M. H.: The Prolongation of the Viability of Cultures of E. Histolytica by the Addition of Streptomycin, J. Parasitol. **33**:416, 1948.

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(Footnote continued on next page)

feres with absorption of the antibiotic.[39] Aureomycin calcium caseinate may be substituted for regular aureomycin to avoid anorexia, nausea and vomiting.[38t] The intravenous route is available for patients unable to take medicaments by mouth (0.5 gm. in 100 to 200 cc. of isotonic sodium chloride solution every 12 hours). Use of the glycinated form of aureomycin and increasing the speed of the injection are reported to diminish the tendency to phlebitis. Carinamide decreases the excretion of aureomycin through the kidneys and may thereby enhance blood levels.[38m] Aureomycin in vitro inhibits many Gram-positive bacteria, including Streptococcus faecalis, and most Gram-negative organisms; Proteus vulgaris and Ps. aeruginosa are consistently resistant.[38b,j]

Clinically, aureomycin when taken as a mouth wash may be useful in the treatment of aphthous stomatitis. The antibiotic is not very effective in typhoid, in typhoid carriers, or in Salmonella and Shigella infections.[40] It has been of value

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Welch, H.: Bacteriologic Studies of Aureomycin, ibid. **51**:211, 1948. (*c*) Collins, H. S.; Paine, T. F., Jr., and Finland, M.: Clinical Studies with Aureomycin, ibid. **51**:231, 1948. (*d*) Little, P. A.: Use of Aureomycin on Some Experimental Infections in Animals, ibid. **51**:246, 1948. (*e*) Dowling, H. F.; Lepper, M. H.; Sweet, L. K., and Brickhouse, R. L.: Studies on Serum Concentrations in Humans and Preliminary Observations on the Treatment of Human Infections with Aureomycin, ibid. **51**:241, 1948. (*f*) Schoenbach, E. B.; Bryer, M. S., and Long, P. H.: The Pharmacology and Clinical Trial of Aureomycin: A Preliminary Report, ibid. **51**:267, 1948. (*g*) Bryer, M. S.; Schoenbach, E. B.; Chandler, C. A.; Bliss, E. A., and Long, P. H.: Aureomycin: Experimental and Clinical Investigations, J. A. M. A. **138**:117, 1948. (*h*) Collins, H. S.; Paine, T. F., Jr.; Wells, E. B., and Finland, M.: Aureomycin: A New Antibiotic; Evaluation of Its Effects in Typhoid Fever, Severe Salmonella Infections, and in a Case of Colon Bacillus Bacteremia, Ann. Int. Med. **29**:1077, 1948. (*i*) Finland, M.; Collins, H. S., and Paine, T. F., Jr.: Aureomycin, A New Antibiotic: Results of Laboratory Studies and of Clinical Use in 100 Cases of Bacterial Infections, J. A. M. A. **138**:946, 1948. (*j*) Paine, T. F., Jr.; Collins, H. S., and Finland, M.: Bacteriologic Studies on Aureomycin, J. Bact. **56**:489, 1948. (*k*) Collins, H. S.: The Clinical Uses of Aureomycin, Bull. New England. M. Center **11**:145, 1949. (*l*) Brainerd, H.; Lennette, E. H.; Meiklejohn, G.; Bruyn, H. B., Jr., and Clark, W. H.: The Clinical Evaluation of Aureomycin, J. Clin. Invest. **28**:992, 1949. (*m*) Sanders, M.; Rumball, J. M.; Solomon, C.; Soret, M. G., and Ricci, N. I.: Further Experiences with Intravenous Aureomycin Therapy: A Study of 116 Cases, ibid. **28**:1006, 1949. (*n*) Spink, W. W., and Yow, E. M.: Aureomycin: Present Status in the Treatment of Human Infections, J. A. M. A. **141**:964, 1949. (*o*) Rose, H. M., and Kneeland, Y., Jr.: Aureomycin in the Treatment of Infectious Diseases, Am. J. Med. **7**:532, 1949. (*p*) Wolgamot, J. R., and Duncan, G. G.: Aureomycin, Chloramphenicol and Terramycin, Pennsylvania M. J. **53**:1262, 1950. (*q*) Herrell, W. E.: Observations on the Clinical Use of Aureomycin, Proc. Staff Meet., Mayo Clin. **24**:612, 1949. (*r*) Dowling, H. F., and Lepper, M. H.: Recent Advances in Antibiotic Therapy with Special Reference to Aureomycin and Chloramphenicol, South. M. J. **43**:190, 1950. (*s*) Neter, E.: The Use and Action of the Newer Antibiotics: Aureomycin, Chloromycetin and Bacitracin, New York J. Med. **50**:79, 1950. (*t*) Manning, P. R., and Wellman, W. E.: Aureomycin Calcium Caseinate: A New Preparation Associated with a Low Incidence of Nausea and Vomiting, Proc. Staff Meet., Mayo Clin. **27**:89, 1952.

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40. Footnote 38*h*, *l*, *n*, and *r*.

in gastroenteritis attributed to Esch. coli var. neapolitana.[41] Aureomycin in vitro inhibits the growth of the cystic and trophozoite forms of E. histolytica [42] primarily by inhibiting the associated bacterial flora; according to Hall, concentrations of 50 γ per milliliter or more are amebicidal. Beneficial effects in acute and chronic intestinal amebiasis were described frequently [43] after the appearance of the report of McVay, Laird, and Sprunt.[43b,c] Both the cysts and the trophozoites are destroyed. According to Gutch,[43d] the rate of relapse does not exceed that observed with other amebicidal compounds. Most and co-workers [43j] obtained encouraging results in 31 of 32 patients with mild amebiasis given 1 or 2 gm. orally for 10 days; the administration of 23 gm. in 9 days was ineffective in 1 person with severe amebic dysentery. Armstrong and colleagues [43k] administered 0.25 gm. by mouth four times daily for 15 days. Symptoms subsided rapidly; the amebae disappeared, and the intestinal lesions healed promptly; however, the rate of relapse was high. Other observers are not impressed with the amebicidal action of aureomycin [44] and recommend the concurrent administration of standard amebicidal drugs.[43j,q] Watt and co-workers [43m] have cultivated strains of E. histolytica resistant to aureomycin. The antibiotic is of little value in amebic infection of the liver.

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Wright and his associates [45] reported encouraging results with aureomycin in ulcerative colitis, especially during the acute stage; symptomatic response was not always accompanied with proctoscopic improvement.[46] The clinical improvement reported by others does not seem striking.[47] In our experience aureomycin has not been very helpful in ulcerative colitis; indeed, recurrence and intensification of symptoms following administration of the antibiotic have been noted frequently. Similar observations have been made in regional enteritis. Lymphogranuloma venereum causes proctitis and rectal stricture resembling ulcerative colitis; aureomycin apparently may facilitate healing of the inflammation; the stricture, as might be expected, is unaffected.[48]

Aureomycin, given in quantities of 750 mg. by mouth four times daily, rapidly suppresses the bacterial flora of the feces [49]; Proteus, Pseudomonas, yeasts, occasional Str. faecalis, and Trichomonas intestinalis (Trichomonas hominis) persist; as with other antibiotics, the effect on the fecal flora is temporary.[49d] Aureomycin has decreased the mortality from peritonitis [50] and by some investigators [50a,e] is

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regarded as the drug of choice in the preoperative and postoperative care of patients undergoing abdominal surgery (0.75 gm. four times daily for three days). The administration of aureomycin intravenously partially suppressed the intestinal flora in both dogs and man [51]; the antibiotic presumably was excreted into the intestinal tract via the salivary glands and the bile. The excretion of urobilinogen in the feces, urine, and bile diminishes during the ingestion of aureomycin, concomitantly with suppression of the coliform bacteria,[52] and may decrease to levels characteristic of complete biliary obstruction. The normal concentrations of urobilinogen may not be restored for several days after discontinuance of antibiotic therapy. Such determinations, consequently, are of little value in assessing hepatic function when performed during antibiotic therapy.

Aureomycin given in moderate amounts orally does not impair hepatic function. However, increased quantities of fat have been observed in the liver (similar findings have been noted with terramycin).[53] Excessive quantities of aureomycin given by both the oral and the intravenous routes apparently caused liver injury in animals (mice, dogs) and in man.[54] The histologic changes were characterized by increased fat and vacuolation and fragmentation of the cytoplasm of hepatic cells, especially in the central portions of the lobule.

According to György and associates,[55] aureomycin prevents or retards hepatic necrosis in rats fed a diet otherwise causing necrosis of the liver. Terramycin,

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and Jumeaux, C. V.: Aureomycin in the Treatment of Peritonitis, Brit. M. J. **1**:271, 1950. (*e*) Wright, L. T.; Schreiber, H.; Metzger, W. I., and Parker, J. W.: Evaluation of Aureomycin Therapy in Peritonitis: Report of 235 Consecutive Cases, Surg., Gynec. & Obst. **92**:661, 1951. (*f*) Schweinburg, F. B.; Rutenburg, A. M.; Milrod, S.; Glotzer, P., and Fine, J.: The Therapeutic Effect of Aureomycin in Experimental Peritonitis in the Dog, Ann. Surg. **133**:208, 1951. (*g*) Altemeier, W. A., and Culbertson, W. R.: Chloramphenicol (Chloromycetin) and Aureomycin in Surgical Infections, J. A. M. A. **145**:449, 1951. (*h*) Rutenberg, A. M.; Jacob, S. W.; Schweinburg, F. B., and Fine, J.: Aureomycin in Treatment of Diffuse Peritonitis, New England J. Med. **246**:52, 1952.

51. Jacobs, S.; Schweinburg, F. B., and Rutenburg, A. M.: Effect of Intravenous Aureomycin on the Intestinal Flora of Dog and Man, Proc. Soc. Exper. Biol. & Med. **78**:171, 1951.

52. Sborov, V. M.; Jay, A. R., and Watson, C. J.: The Effect of Aureomycin on Urobilinogen Formation and the Fecal Flora, J. Lab. & Clin. Med. **37**:52, 1951. Robbins, W. C.: Depression of Fecal Urobilinogen by Aureomycin and by Terramycin, Proc. Soc. Exper. Biol. & Med. **77**:158, 1951. Galt, J., and Hunter, R. B.: The Effect of Aureomycin on Certain Liver Function Tests and Blood Coagulation, Am. J. M. Sc. **220**:508, 1950.

53. Sborov, V., and Sutherland, D. M.: Fatty Liver Following Aureomycin and Terramycin Therapy in Chronic Hepatic Disease, Gastroenterology **18**:598, 1951. Yesner, R., and Kunkel, P.: Preliminary Observations on the Effect of Aureomycin, Terramycin, Tibione, Combined Tibione and Streptomycin and Chloromycetin on the Morphology of the Liver in Man, Yale J. Biol. & Med. **23**:299, 1950-1951.

54 Lepper, M. H.; Wolfe, C. K.; Zimmerman, H. J.; Caldwell, E. R., Jr.; Spies, H. W., and Dowling, H. F.: Effect of Large Doses of Aureomycin on Human Liver, A. M. A. Arch. Int. Med. **88**:271, 1951. Lepper, M. H.; Zimmerman, H. J.; Carroll, J.; Caldwell, E. R., Jr.; Spies, H. W.; Wolfe, C. K., and Dowling, H. F.: Effect of Large Doses of Aureomycin, Terramycin, and Chloramphenicol on Livers of Mice and Dogs, ibid. **88**:284, 1951.

55. (*a*) György, P.; Stokes, J., Jr.; Smith, W. H., and Goldblatt, H.: Studies on the Use of Aureomycin in Hepatic Disease: II. The Effect of Aureomycin on Experimental Dietary Hepatic Necrosis, Am. J. M. Sc. **220**:6, 1950. (*b*) György, P.; Stokes, J., Jr.; Goldblatt, H., and Popper, H.: Antimicrobial Agents in the Prevention of Dietary Hepatic Injury (Necrosis, Cirrhosis) in Rats, J. Exper. Med. **93**:513, 1951.

streptomycin, and sulfaguanidine afford less protection; penicillin, chloramphenicol, and polymyxin are ineffective. The mechanism of action is not known but may be related to the antimicrobial effect of aureomycin upon the intestinal flora. The influence of aureomycin in hepatic disease thus far has been difficult to evaluate in view of the other therapeutic measures employed simultaneously. Early administration of aureomycin in acute viral hepatitis is recommended,[56] but Shaffer and co-workers [57] observed no clinical or chemical improvement in 37 patients. Favorable results are described occasionally in chronic hepatitis [58] and in hepatic coma. Further studies seem indicated, but our experience with aureomycin in a small group of patients with severe hepatitis and coma has not been encouraging thus far.

Aureomycin is excreted by the normal liver into the bile in high concentrations [59]; excretion is diminished in the presence of poor hepatic function or obstruction of the cystic duct. The antibiotic thus may be useful, when there is no interference with the flow of bile, in the treatment of infections of the biliary tract and in prevention of ascending cholangitis and hepatitis. Aureomycin has been effective in patients with acute cholecystitis,[49b] cholangitis,[60] and biliary fistula [61]; Esch. coli usually was the infecting organism. In a patient with recurrent cholangitis and liver abscesses caused by Bacteroides funduliformis, resistance to aureomycin had not developed after four months of successful treatment.[62] Recent studies emphasize the value of aureomycin orally in the treatment of experimental acute pancreatitis in dogs [63]; the superiority of oral over intravenous administration suggests that organisms invading the tissues from the intestine after the onset of the

56. McNeile, H. J., and Solomon, C.: Aureomycin in Acute Fulminant Hepatitis: Report on Successful Treatment in 3 Cases, New York J. Med. **50**:1393, 1950. Rissel, E.: Aureomycin in Treatment of Epidemic Hepatitis and Related Forms of Jaundice, Helvet. med. acta **17**:404, 1950.

57. György and others.[55a] Shaffer, J. M.; Farquhar, J. D.; Stokes, J., Jr., and Sborov, V. M.: Studies on the Use of Aureomycin in Hepatic Disease: I. Aureomycin Therapy in Acute Viral Hepatitis, Am. J. M. Sc. **220**:1, 1950. Farquhar, J. D.; Stokes, J., Jr.; Whitlock, C. M., Jr.; Bluemle, L. W., Jr., and Gambescia, J. M.: Studies on the Use of Aureomycin in Hepatic Disease: III. A Note on Aureomycin Therapy in Hepatic Coma, ibid. **220**:166, 1950. Shaffer, J. M.; Bluemle, L. W., Jr.; Sborov, V. M., and Neefe, J. R.: Studies on the Use of Aureomycin in Hepatic Disease: IV. Aureomycin Therapy in Chronic Liver Disease, with a Note on Dermal Sensitivity, ibid. **220**:173, 1950.

58. György and others.[55] Rumball, J. M.; Marion, D. F., and Sanders, M.: Post-Hepatitic Cirrhosis Treated with Aureomycin: A Case Report, Gastroenterology **14**:432, 1950. Goldbloom, R. S., and Steigmann, F.: Aureomycin Therapy in Hepatic Insufficiency, ibid. **18**:93, 1951.

59. Zaslow, J.; Hewlett, T. H., and Lorry, R. W.: The Excretion and Concentration of Aureomycin in the Abnormal Human Biliary Tract: I. Gallbladder, Gastroenterology **16**:475, 1950. Zaslow, J.; Hewlett, T. H., and Goldsmith, R.: The Excretion and Concentration of Aureomycin in the Abnormal Human Biliary Tract: II. Hepatic Bile, ibid. **16**:479, 1950.

60. Rutenburg and others.[49i] Wright, L. T., and Prigot, A.: Aureomycin as an Aid in Abdominal Surgery, Ann. Surg. **133**:364, 1951.

61. Brainerd, H.; Lennette, E. H.; Meiklejohn, G.; Bruyn, H. B., Jr., and Clark, W. H.: The Clinical Evaluation of Aureomycin, J. Clin. Invest. **28**:992, 1949.

62. Rubin, S. H.; Bernstein, P. K.; Perrine, C.; Rubin, A. D., and Schwimmer, D.: Aureomycin Treatment of Recurrent Cholangitis with Liver Abscesses Due to Bacteroides Funduliformis, Ann. Int. Med. **38**:468, 1951.

63. Persky, L.; Schweinburg, F. B.; Jacob, S., and Fine, J.: Aureomycin in Experimental Acute Pancreatitis of Dogs, Surgery **30**:652, 1951.

pancreatitis are implicated in the fatal outcome. Aureomycin also appears to be helpful in the treatment of fibrocystic disease of the pancreas, as observed in 17 children treated for periods of 12 to 24 months [64]; the mechanism of action is not known.

Aureomycin may cause important side-effects.[65] Gastrointestinal symptoms include nausea, vomiting, substernal distress, dysphagia, and soft, bulky stools. Glossitis, stomatitis, esophagitis, gastritis, proctitis, and colitis may develop. The nausea and vomiting are not correlated with changes in the gastroscopic appearance of the gastric mucosa, although in one patient an erosive hemorrhagic gastritis subsided after the discontinuance of aureomycin therapy.[65e] The oral lesions have been described more frequently in women and in patients with poor intake of food.[65b] It has been suggested that aureomycin promotes vitamin deficiency by altering the intestinal flora, the destruction of bacteria presumably interfering with the synthesis of vitamins of the B complex; other, as yet unidentified, metabolic changes may occur. Merliss and Hoffman [66] have adduced clinical evidence of steatorrhea during the use of aureomycin; similar findings were noted after administration of terramycin, chloramphenicol, and the combination of penicillin and sulfonamides. The steatorrhea is attributed to dysfunction of the small bowel in conjunction with a deficiency state; treatment with liver extract and vitamin B seems helpful. The proctitis and colitis may be severe; in some cases the diarrhea has seriously disturbed electrolyte and fluid balance.[49l] Our experience has been similar; the clinical syndrome and proctoscopic changes in several patients were indistinguishable from that of so-called nonspecific ulcerative colitis. Indeed, these side-effects at times have been so disturbing as to cause us to limit the use of aureomycin. Perhaps the administration of smaller doses, 250 mg. every six hours, will prove less distressing to the gastrointestinal tract.

Aureomycin, like other antibiotics, also changes the normal bacterial flora of the mouth and vagina. Infection of the mouth, vagina, and rectum with Monilia

64. Stowens, D.: Aureomycin in the Treatment of Fibrocystic Disease of the Pancreas, Pediatrics **8**:60, 1951.

65. (*a*) Footnote 38*l*, *q*, and *r*. (*b*) Rutenburg and others.[49l] (*c*) Peck, S. M., and Feldman, F. F.: Sensitivity Reactions to Aureomycin, J. A. M. A. **142**:1137, 1950. (*d*) Behrman, H. T.: Pruritus Vulvae Due to Aureomycin, ibid. **144**:995, 1950. (*e*) Lewis, C. S., Jr.; Bauerlein, T. C., and Shytles, H. M., Jr.: Effect of Aureomycin on the Stomach: A Gastroscopic Study, Gastroenterology **16**:586, 1950. (*f*) Pappenfort, R. B., Jr., and Schall, E. S.: Moniliasis in Patients Treated with Aureomycin, A. M. A. Arch. Int. Med. **88**:729, 1951. (*g*) Weyler, H. L. C.: Skin Irritation Around the Anus Due to Aureomycin, Rhode Island M. J. **33**:137, 1950. (*h*) Tomaszewski, T.: Side Effects of Chloramphenicol and Aureomycin with Special Reference to Oral Lesions, Brit. M. J. **1**:388, 1951. (*i*) Bedford, P. D.: Idiosyncrasy to Aureomycin, ibid. **1**:1428, 1951. (*j*) Gewin, H. M., and Friou, G. J.: Manifestations of Vitamin Deficiency During Aureomycin and Chloramphenicol Therapy of Endocarditis Due to Staphylococcus Aureus, Yale J. Biol. & Med. **23**:332, 1951. (*k*) Curtis, V. J.; Giliberti, J. J., and Schraft, W. C.: Esophagogastritis Complicating Aureomycin Therapy, New York J. Med. **51**:1195, 1951. (*l*) Welsh, A. L., and Goldberg, L. C.: Fixed Drug Eruption from Aureomycin: Report of 2 Cases, A. M. A. Arch. Dermat. & Syph. **64**:356, 1951. (*m*) Yow, E. M.: Aureomycin Therapy in Bacterial Infections Resistant to Penicillin and Streptomycin, Texas J. Med. **46**:694, 1950.

66. Merliss, R. R., and Hoffman, A.: Steatorrhea Following the Use of Antibiotics, New England J. Med. **245**:328, 1951.

(Candida) albicans is a common and annoying complication.[67] Modification of the bacterial flora also may be complicated by superinfection with previously nonpathogenic organisms; for example, infection of the urinary tract with P. vulgaris. Other untoward effects reported in the literature include allergic skin manifestations, anaphylaxis in a patient sensitive also to acetylsalicylic acid and penicillin,[65i] neutropenia,[38o] and prothrombin deficiency and peripheral and optic neuritis [65j] in a patient also receiving chloramphenicol. The use of smaller amounts of aureomycin, perhaps 250 mg. every two hours for eight doses daily, has been suggested to decrease the incidence of side-effects. Bacterial resistance to aureomycin develops in vitro after repeated transfer of S. typhi and P. vulgaris to media containing increasing concentrations of the antibiotic. Cross resistance among aureomycin, chloramphenicol, and terramycin also has been demonstrated. The problem of cross resistance to antibiotics has been studied extensively by Jawetz and associates [68] and by Gocke and Finland.[69] Bacterial resistance develops more slowly to aureomycin than to streptomycin and thus far has been encountered in man only occasionally.

CHLORAMPHENICOL

Chloramphenicol (chloromycetin®) is obtained from filtrates of cultures of Streptomyces venezuelae.[70] It also has been chemically synthesized in pure crystalline form. Chloramphenicol is readily absorbed from the gastrointestinal tract after oral administration; a palatable suspension (chloromycetin® palmitate) [71] has been prepared. The antibiotic may be given intravenously, using acetyldimethylamine as a solvent.[72] Its antibacterial spectrum resembles that of aureomycin.[70c,d]

67. Footnote 65*d*, *f*, and *h*.

68. Jawetz, E.; Gunnison, J. B., and Coleman, V. R.: The Combined Action of Penicillin with Streptomycin or Chloromycetin on Enterococci in Vitro, Science **111**:254, 1950. Jawetz, E., and Speck, R. S.: Joint Actions of Penicillin with Chloramphenicol on an Experimental Streptococcal Infection of Mice, Proc. Soc. Exper. Biol. & Med. **74**:93, 1950. Gunnison, J. B.; Coleman, V. R., and Jawetz, E.: Interference of Aureomycin and of Terramycin with Action of Penicillin in Vitro, ibid. **75**:549, 1950. Gunnison, J. B.; Jawetz, E., and Coleman, V. R.: The Effect of Combinations of Antibiotics on Enterococci in Vitro, J. Lab. & Clin. Med. **36**:900, 1950.

69. Gocke, T. M., and Finland, M.: Cross-Resistance to Antibiotics: Effect of Repeated Exposure of Bacteria to Aureomycin, Terramycin, Chloramphenicol or Neomycin on the Resistance to All of These Antibiotics and to Streptomycin, J. Lab. & Clin. Med. **38**:719, 1951.

70. (*a*) Woodward, T. E.: Chloromycetin and Aureomycin: Therapeutic Results, Ann. Int. Med. **31**:53, 1949. (*b*) Woodward, T. E.; Parker, R. T., and Hall, H. E.: Therapeutic Results with Aureomycin and Chloramphenicol, Bull. New York Acad. Med. **26**:66, 1950. Smadel, J. E.: (*c*) Chloramphenicol (Chloromycetin) in the Treatment of Infectious Diseases, Am. J. Med. **7**:671, 1949; (*d*) Clinical Use of the Antibiotic Chloramphenicol (Chloromycetin), J. A. M. A. **142**:315, 1950.

71. McLean, I. W.; Schwab, J. L.; Hillegas, A. B., and Schlinguran, A. S.: Susceptibility of Micro-Organisms to Chloramphenicol (Chloromycetin), J. Clin. Invest. **28**:953, 1949.

72. Larkin, V. deP.: Chloromycetin Palmitate: Its Use in Pediatrics, Proc. Soc. Exper. Biol. & Med. **78**:191, 1951. Orr, W. W.: Evaluation of Intravenous Chloramphenicol: A Preliminary Report, Antibiotics & Chemother. **1**:63, 1951. Moseley, V., and Baroody, W. G.: Report on Safety and Therapeutic Effectiveness of Parenterally Administered Chloromycetin by Intramuscular and Intravenous Routes, South Carolina M. A. J. **47**:157, 1951.

Chloramphenicol is the antibiotic of choice in treatment of typhoid.[73] Clinical improvement is apparent within 24 to 48 hours; the temperature returns to normal within three or four days, and the blood cultures become negative rapidly. Approximately 25 to 30 gm. should be administered over two weeks. The initial oral dose is 50 mg. per kilogram of body weight, followed by 0.75 gm. every six hours until

73. (*a*) Burnell, J. M., and Kirby, W. M. M.: Serum Concentrations of Chloramphenicol Following Intravenous and Intramuscular Administration, J. Lab. & Clin. Med. **38**:234, 1951. (*b*) Woodward, T. E.; Smadel, J. E.; Ley, H. L., Jr.; Green, R., and Mankikar, D. S.: Preliminary Report on the Beneficial Effect of Chloromycetin in the Treatment of Typhoid Fever, Ann. Int. Med. **29**:131, 1948. (*c*) Bradley, W. H.: Chloromycetin in Typhoid Fever, Lancet **1**:869, 1949. (*d*) Christie, A. B.: Chloromycetin, Postgrad. M. J. **25**:410, 1949. (*e*) Collins, H. S., and Finland, M.: Treatment of Typhoid Fever with Chloromycetin, New England J. Med. **241**:556, 1949. (*f*) Cook, A. T., and Marmois, D. E.: Chloromycetin in the Treatment of Typhoid Fever, Lancet **2**:975, 1949. (*g*) Douglas, A. D. M.: Typhoid Fever, Treated with Chloramphenicol: Development of the Carrier State, ibid. **1**:858, 1950. (*h*) Briggs, J. N.: Relapse in Typhoid Fever After Treatment with Chloramphenicol, ibid. **1**:115, 1950. (*i*) El Ramli, A. H.: Chloramphenicol in Typhoid Fever, ibid. **1**:618, 1950. (*j*) Smadel, J. E.; Bailey, C. A., and Lewthwaite, R.: Synthetic and Fermentation Type Chloramphenicol (Chloromycetin) in Typhoid Fever: Prevention of Relapses by Adequate Treatment, Ann. Int. Med. **33**:1, 1950. (*k*) Woodward, T. E.; Smadel, J. E., and Ley, H. L., Jr.: Chloramphenicol and Other Antibiotics in the Treatment of Typhoid Fever and Typhoid Carriers, J. Clin. Invest. **29**:87, 1950. (*l*) Smadel, J. E.; Ley, H. L., and Diercks, F. H.: Treatment of Typhoid Fever: I. Combined Therapy with Cortisone and Chloramphenicol, Ann. Int. Med. **34**:1, 1951. (*m*) Jacobsen, L. Y., and Broderick, R. A.: Chloromycetin in the Treatment of Typhoid Fever, ibid. **32**:775, 1950. (*n*) Ruiz Sanchez, F.: Treatment of Typhoid Fever with Aureomycin and Chloromycetin, M. Medicina, México **30**:115, 1950. (*o*) Feldman, N., and Selby, S.: Chloromycetin Therapy in Typhoid Fever in Bantu Children, South African J. Clin. Sc. **1**:149, 1950. (*p*) Matteucci, W. V.; Schimmel, N. H., and Boger, W. H.: Typhoid Fever: Chloramphenicol Therapy and the Problem of Relapse, Am. J. M. Sc. **222**:446, 1951. (*q*) Jenson, R. L., and Spicer, W. E.: Typhoid Fever Treated with Chloromycetin: Report of Case, Kansas M. Soc. J. **51**:565, 1950. (*r*) Meneghello, J.; Undurraga, O., and Raimann, A.: Chloramphenicol in the Treatment of Children with Typhoid Fever, Rev. chilena pediat. **21**:535, 1950. (*s*) Benhamou, E.; Destaing, F., and Sorrel, A.: General Remarks on 300 Cases of Typhoid Fever Treated with Chloramphenicol (Chloromycetin) Combined with Other Antibiotics, Semaine hôp. Paris **26**:4107, 1950. (*t*) Laporte, A.; Fritel, D.; Ricordeau, G., and Betourne, C.: Problem of Relapse in Typhoid and Paratyphoid Fever in Patients Treated with Chloramphenicol (Chloromycetin), Presse méd. **58**:989, 1950. (u) Mollaret, P.: Usefulness and Hazards of Treatment of Typhoid and Paratyphoid Fever with Chloramphenicol (Chloromycetin), Wien. klin. Wchnschr. **62**:381, 1950. (*v*) Medina, I.; Payne, E. H., and Sharp, E. A.: Typhoid and Chloromycetin Study of Minimum Dosage, J. Trop. Med. **53**:119, 1950. (*w*) Sédallion, P.; Maral, R.; Exbrayat, C.; Traeger, J., and Gaillard, L.: Chloramphenicol in Treatment of Typhoid Fever, J. méd. Lyon **31**:627, 1950. (*x*) Rumball, C. A., and Moore, L. G.: Treatment of a Chronic Typhoid Carrier with Chloromycetin, Brit. M. J. **1**:943, 1949. (*y*) Crocker, T. T., and Gelperin, A.: Treatment of the Typhoid Carrier State with Chloramphenicol, Yale J. Biol. & Med. **23**:119, 1950-1951. (*z*) Furbetta, D., and Bufolari, A.: Clinical and Immunologic Aspects of Course of Typhoid After Chloramphenicol Treatment, Sett. méd. **39**:125, 1951. (*a'*) Farinaud, M. E., and Portes, L.: Chloramphenicol (Chloromycetin) in Progressive Doses in Treatment of Typhoid Fever of Hypertoxic Type, Presse méd. **59**:3, 1951. (*b'*) Häring, F. O.: Mechanism of Action of Aureomycin and Chloromycetin in Rickettsial and Typhoid Diseases, Klin. Wchnschr. **29**:49, 1951. (*c'*) Gruhzit, O. M., and Fisken, R. A.: Effect of Chloromycetin on Experimental S. Typhosa Infection in Rabbits, Am. J. Trop. Med. **31**:329, 1951. (*d'*) Mond, I.: Use of Chloramphenicol and Typhoid Vaccine in Infant Born of Typhoid Carrier, J. A. M. A. **147**:249, 1951. (*e'*) Gaub, W. H.: An Epidemic of Typhoid Fever at Spinard, Alaska, J. Lab. & Clin. Med. **37**:924, 1951.

the temperature is normal; therapy is continued with 0.5 gm. every six hours for a total of 14 days of treatment. Symptomatic improvement is more rapid when cortisone is given simultaneously; however, two of eight patients relapsed during the period of observation.[73l] Chloramphenicol is not always effective. Matteucci and co-workers [73p] described three patients treated with chloramphenicol in whom the course was characterized by relapses, persistently positive fecal cultures, and delayed defervescence; they recommend antibiotic therapy for a period corresponding with the average duration of unmodified typhoid. Hemorrhage and perforation may occur.[74] Development of the chronic carrier state is not prevented.[75] In two carriers little or no active chloramphenicol was found in the bile obtained by duodenal intubation despite treatment for two or more weeks; the bile contained large numbers of typhoid bacilli.[73y] The occurrence of severe, occasionally fatal, toxemia has been attributed to the massive disintegration of typhoid bacilli and the liberation of large amounts of endotoxin.[76] Chloramphenicol failed to abort acute infection with S. typhi in rabbits; its effect against the carrier state was relatively slight.[73c'] The evidence to date thus suggests that chloramphenicol suppresses the growth of the typhoid organism; ultimate recovery is dependent upon the development of immunity in the host.[73k]

Other investigators have studied results of chloramphenicol therapy in paratyphoid, Salmonella, and Shigella infections.[77]

Results appear satisfactory in some Salmonella infections (those due to Type Montevideo,[77k] S. paratyphi B,[77a,i] S. typhimurium,[77e] S. morbificans) and unfavorable in others [77m,n] (infections due to Types San Diego, Oranienburg, Braenderup,[77l]

74. Woodward.[70a] Smadel and others.[73j]

75. Footnote 23*e*, *k*, and *t*.

76. Footnote 73*u*, *w*, *y*, and *a'*.

77. (*a*) Curtin, M.: Paratyphoid B. Fever Treated with Chloramphenicol, Brit. M. J. **2**:1504, 1949. (*b*) Clément, R.; Gerbeaux, J.; Combes-Hamelle, A.; Masse, N. P., and Tetu, M. A.: Treatment of Severe Infant Diarrhea with Chloromycetin, Presse méd. **58**:444, 1950. (*c*) Ross, S.; Burke, F. G.; Rice, E. C.; Washington, J. A., and Stevens, S.: Chloromycetin in Treatment of Salmonella Enteritis, New England J. Med. **242**:173, 1950; (*d*) Chloramphenicol (Chloromycetin) Therapy in Shigella Enteritis, J. A. M. A. **143**:1459, 1950. (*e*) Scott, E. G.: Bacillary Dysentery and Gastroenteritis: Diagnosis and Treatment of 18 Cases, Delaware M. J. **22**:9, 1950. (*f*) Cooper, M. L., and Keller, H. M.: Dysentery Due to Sulfonamide-Resistant Shigella Sonnei Controlled with Chloromycetin, Am J. Dis. Child. **80**:911, 1950. (*g*) Birdsong, M.; Mitchell, J. E., and Waddell, W. W., Jr.: Typhoid and Paratyphoid Fever: A Review of 4 Cases Treated with Chloromycetin, J. Pediat. **36**:310, 1951. (*h*) Fison, D. C., and Singer, E.: Treatment of Gastroenteritis in Infants with Chloromycetin, M. J. Australia **2**:957, 1950. (*i*) Galpine, J. F., and Brown, J. W.: Two Cases of Paratyphoid Fever Treated with Chloramphenicol, Brit. M. J. **2**:819, 1950. (*j*) Mazursky, M. M.: A Clinical Trial with Chloromycetin in Shigella Dysenteriae (Sonne): Report of 3 Cases, J. Pediat. **37**:238, 1950. (*k*) Hines, J. J.: Treatment of Salmonella Septicemia with Chloramphenicol, J. A. M. A. **147**:248, 1951. (*l*) Weiner, H. A., and Liebler, J. B.: Infections with Multiple Salmonella Types, Including S. Braenderup: Results of Chloramphenicol Treatment, ibid. **145**:802, 1951. (*m*) Seligman, E., and Wasserman, M.: Action of Chloromycetin on Salmonella, Proc. Soc. Exper. Biol. & Med. **71**:253, 1949. (*n*) Neva, F. A.; Nelson, R. J., and Finland, M.: Hospital Outbreaks of Infections with Salmonella Newington, New England J. Med. **244**:252, 1951. (*o*) Smellie, J. M.: Chloromycetin in Infantile Gastroenteritis, Proc. Roy. Soc. Med. **43**:766, 1950. (*p*) Epstein, H. C.; Hochwald, A., and Ashe, R.: Salmonella Infections of the New Born Infant, J. Pediat. **38**:723, 1951. (*q*) Copping, G. A., and Reed, R. W.: Septicemia Due to Salmonella San Diego, Canad. M. A. J. **64**:528, 1951.

and Newington [77m,n]). Chloramphenicol was effective in Shigella infections resistant to sulfadiazine (due to S. sonnei and S. paradysenteriae [S. flexneri] [77f] and in an outbreak of gastroenteritis attributed to Bacterium coli B.G.T. (Bray, Giles, and Taylor).[78] The antibiotic is amebicidal in vitro; it temporarily controlled experimental amebic colitis in dogs.[79] Clinical results have been disappointing thus far, except in a group of "healthy carriers."[80] Like aureomycin, and terramycin, it is ineffective against Giardia lamblia, whipworm, and hookworm. It is apparently of value in the proctitis caused by lymphogranuloma venereum.[81]

According to Bercovitz,[82] chloramphenicol, in doses of 3 gm. by mouth daily, is useful in ulcerative colitis. Our experience has been less favorable. Like aureomycin, chloramphenicol decreases the bacterial counts in the feces of both normal persons and patients with ulcerative colitis by suppressing coliform organisms and Str. faecalis. This effect is maintained for approximately two weeks and then wanes despite continued treatment.[49d] Chloramphenicol thus far seems of little or no value in treatment of acute viral hepatitis.[83] This antibiotic does not appear to be excreted in the bile in a biologically active form.

Therapeutic doses of chloramphenicol do not impair hepatic or renal function. The antibiotic causes gastrointestinal symptoms similar to those described for aureomycin. The literature also contains references to the development of a mild euphoric state, anaphylactic shock,[84] granulocytopenia, mild hemolytic anemia, fatal aplastic anemia,[85] and avitaminosis.[86] The development of bacterial resistance to chloramphenicol has been demonstrated in vitro.[87] Bacterial resistance also has been encountered clinically in patients treated for infections of the urinary tract;

78. Rogers, K. B.; Koegler, S. J., and Gerrard, J.: Chloramphenicol in Treatment of Infantile Gastro Enteritis: A Preliminary Report, Brit. M. J. **2**:1501, 1949.

79. Thompson, P. E.; Dunn, M. C.; Bayles, A., and Reinertson, J. W.: Action of Chloramphenicol (Chloromycetin) and Other Drugs Against Endamoeba Histolytica in Vitro and in Experimental Animals, Am. J. Trop. Med. **30**:203, 1950.

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in most instances the resistance was associated with therapeutic failure.[88] Increasing resistance of typhoid organisms to the antibiotic was demonstrated in vitro with a strain from a patient who relapsed during therapy.[89] As with other antibiotics, resistance probably results from the process of drug selection and successive mutations of rare drug-fast variants existing in an otherwise susceptible species of bacteria. Jawetz and his associates [90] have adduced evidence that chloramphenicol, like aureomycin and terramycin, may interfere with the action of streptomycin.

TERRAMYCIN

Terramycin [91] is prepared from the growth of the actinomycete, Streptomyces rimosus. It is readily absorbed from the gastrointestinal tract after oral administration [91o]; food does not decrease blood levels, but aluminum hydroxide interferes

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(Footnote continued on next page)

with absorption.[91a] Terramycin buffered with sodium glycinate may be given intravenously in doses of 0.5 to 1 gm. every 12 hours. The antibacterial spectrum of terramycin resembles that of aureomycin and chloramphenicol[92]; according to some observers it is more effective than the other two antibiotics against Esch. coli and Salmonella.

Favorable results have been reported in the treatment of bacillary dysentery,[93] of bacteremia with S. choleraesuis,[94] and of an infection attributed to Esch. coli serotype D433.[95] Terramycin was effective also in four patients with Salmonella infections resistant to chloramphenicol (caused by Salmonella sp. [Type Newington and Type Oranienburg]).[91f] It does not appear to be of value in typhoid, ulcerative colitis, and regional enteritis, although benefit may be observed occasionally.[96] Failures are reported in infections with Proteus and Pseudomonas organisms and in one patient with infection due to S. choleraesuis.[91b] S. typhi persisted in the feces of 12 chronic carriers after the oral administration of 1.25 gm. of chloramphenicol every six hours for 10 days.[97]

Terramycin is highly active against E. histolytica in culture.[98] In doses of 2 or 3 gm. daily for 10 days, it is reportedly effective in intestinal amebiasis, perhaps more so than aureomycin.[99] Most, in a series of 54 patients, encountered several

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92. Footnote 91*e*, *l*, and *m*.

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recurrences, all with hepatic involvement; other investigators have had a similar experience. Other intestinal amebae, Endamœba coli, Endoliamax nana, and Iodamœba buetschlii, also may be eliminated during terramycin therapy. The antibiotic seems helpful in the treatment of pinworm [100] and Ascaris infestation. Terramycin is excreted in high concentrations in the bile and is regarded by some investigators as the antibiotic of choice in the treatment of acute or chronic cholangitis. Favorable clinical results have been reported in patients with acute cholecystitis,[101] cholangitis,[102] and hepatitis,[103] but the number of cases is small.

The effect of terramycin on the fecal flora resembles that of aureomycin.[104] The coliform organisms are eliminated rapidly; Str. faecalis is suppressed in 50% of cases; the fecal flora is replaced by a heavy growth of P. vulgaris, Proteus morganii, and yeasts. The bacterial flora rapidly returns to its original state after discontinuance of therapy. Among patients being prepared for intestinal surgery, prothrombin was not significantly altered in the presence of pronounced reduction in the number of intestinal bacteria following the oral administration of terramycin.[104d] Terramycin, according to Pulaski and his associates,[104f] is highly effective in the treatment of experimental and clinical peritonitis.

The side-effects are similar to those noted with aureomycin and chloramphenicol. Gastrointestinal symptoms develop in many patients; occasionally they necessitate discontinuance of therapy. Anorectal burning, soreness, and pruritus are not uncommon and presumably are related to the alteration in intestinal flora.[105]

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105. Wilcox, R. R.: Anorectal Syndrome and Other Mild Side Effects of Terramycin, Lancet **2**:153, 1951.

NEOMYCIN

Neomycin is produced by two strains of Streptomyces fradiae.[106] It may be administered intramuscularly or orally in doses of 0.5 gm. four times daily; the antibiotic is not absorbed from the gastrointestinal tract. It is active in vitro against Gram-positive and Gram-negative bacteria, including streptomycin-resistant strains,[107] and has been described as the most effective of all antibiotics against E. histolytica in culture.[108]

The use of neomycin in gastrointestinal disease thus far has been limited. Favorable results are reported in the treatment of Shigella and Salmonella infections, and amebiasis,[109] peritonitis, and appendiceal abscess.[110] According to Poth and co-workers and others,[111] neomycin effectively suppresses the fecal flora; further studies of this problem are in progress.

The intramuscular administration of neomycin causes renal injury, with the appearance of albumin and casts in the urine,[12] and damage to the eighth cranial nerve, resulting first in deafness,[113] then in disturbance of the vestibular apparatus.

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112. Waisbren, B. A., and Spink, W. W.: A Clinical Appraisal of Neomycin, Ann. Int. Med. **33**:1099, 1950.

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Nausea and diarrhea also may occur. The oral administration of neomycin apparently does not cause toxic effects. Bacterial resistance to neomycin has been produced experimentally [114]; its clinical occurrence has been noted in several cases.[111c] Organisms rendered resistant to neomycin in vitro did not manifest an increase in resistance to aureomycin, chloramphenicol, or terramycin.

BACITRACIN

Bacitracin is derived from a strain of Bacillus subtilis, recovered from the débrided tissue of a compound fracture.[115] It is characterized chemically as a diffusible polypeptide of low molecular weight. Bacitracin is administered locally in the treatment of pyoderma and superficial infections and orally in certain gastrointestinal diseases; the intramuscular and intravenous routes now are employed less frequently. Its antibacterial spectrum parallels that of penicillin and includes strains resistant to penicillin; it also inhibits the growth in vitro of Esch. coli, S. typhi, Aerobacter aerogenes, P. vulgaris, and E. histolytica.

Bacitracin orally has been effective in chronic Shigella dysentery.[116] Satisfactory results were obtained in 48 of 51 patients with amebiasis receiving 40,000 to 120,000 units by mouth daily.[117] However, it seems less effective than aureomycin or terramycin, and the simultaneous use of other amebicidal drugs has been recommended. Bacitracin is not absorbed from the gastrointestinal tract; hence, it is of no value in amebic hepatitis. Clinical improvement has been reported occasionally in ulcerative colitis treated with bacitracin alone or together with streptomycin and glucuronolactone [118]; experience with this antibiotic as yet is too limited to warrant an opinion. Its effect in regional enteritis has been indifferent.[118] Bacitracin orally apparently cured two patients with enteritis caused by Balantidium coli.[119] Local

114. Wolgamot, J. R., and Duncan, G. G.: The Clinical Use of Neomycin, Pennsylvania M. J. **53**:1264, 1950.

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application of bacitracin resulted in the healing of multiple liver abscesses produced by anaerobic Streptococcus viridans, developing after removal of a gangrenous appendix; many other antibiotics had been ineffective. Varying results have been reported in studies of the fecal flora. In the dog, the streptococci and spore-forming anaerobes decreased and the coliform organisms were unaffected.[119] In man, bacitracin, together with streptomycin and glucuronolactone, eliminated Gram-positive bacteria and partially decreased the number of Esch. coli.[120]

Bacitracin when given intramuscularly or intravenously has caused renal injury, characterized clinically by proteinuria and casts, functionally by acute depression of tubular and possibly glomerular function, and pathologically by renal tubular necrosis.[121] The tendency to renal damage may be decreased by the administration of alkali sufficient to raise the pH of the urine to 6.0 or higher. Improved methods of preparation may decrease the toxic effects on the kidney. Minimal side-effects have been described after the oral ingestion of bacitracin; these include abdominal distress, anorexia, nausea, headache, transient skin eruptions, and pruritus ani.[121]

POLYMYXIN

Polymyxin is the generic term for a group of antibiotics derived from Bacillus polymyxa (Bacillus aerosporus), a spore-forming rod occurring in the soil.[122] The various polymyxins, designated as A, B, C, D, and E, have been characterized chemically as relatively simple basic polypeptides, forming water-soluble salts with mineral acids. Their antibacterial spectra are similar, and they differ only in their amino acid content. The polymyxins in vitro are the most powerful of all antibiotics against Gram-negative bacteria, especially Ps. aeruginosa[123]; variable results have been reported with E. histolytica. Polymyxin B is the usual preparation for clinical application; 15 to 20 mg. per kilogram of body weight daily for 10 days has been suggested as the oral dose.

Polymyxin B orally has yielded very favorable results in infections with Ps. aeruginosa and Esch. coli, in bacillary dysentery[124] (especially chronic dysen-

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tery [125]), and in typhoid carriers. Indifferent or negligible effects have been reported for "nonspecific enteritis," typhoid, Salmonella infections, and amebiasis. Polymyxin orally, even in doses as small as 50 mg., appears to be a potent intestinal "antiseptic" in man; all coliform bacteria except Proteus organisms are suppressed within 24 to 60 hours; the bacteriostatic effect apparently persists for a longer period than with other antibiotics.[126]

The polymyxins may cause serious reactions when given intramuscularly.[127] Polymyxin B is considered less toxic than polymyxin D, but opinions vary. Renal tubular damage is manifested by albumin, red and white blood cells, and granular casts in the urine and is severer in patients with preexisting renal impairment. Neurologic symptoms include weakness, drowsiness, ataxia, numbness of the fingers and toes, impaired position sense, and blurring of vision with diplopia and nystagmus; these manifestations are described as mild and transitory. Polymyxins also may cause allergic reactions characterized by intense itching about the mouth and face, urticaria, and a maculopapular rash; antihistaminic drugs relieve these symptoms. Toxic effects have not been described after the topical or oral administration of polymyxin B; the antibiotic is not absorbed in significant amounts from the gastrointestinal tract.

MULTIPLE ANTIBIOTIC THERAPY

The simultaneous use of two or more antibiotics may be more effective in certain instances than the administration of the same compounds individually in identical or larger amounts.[128] Multiple antibiotic therapy, according to Dowling, may have the following advantages: (1) improved prospects of cure in mixed bacterial infections; several antibiotics each may act against separate components of the mixed flora (e. g., streptomycin and bacitracin for intestinal antisepsis; penicillin and streptomycin in peritonitis [129]); (2) prevention of superinfection during single antibiotic therapy; (3) prevention of side-effects from large amounts of one antibiotic by administering smaller quantities of several compounds; (4) delay or prevention of bacterial resistance (e. g., streptomycin and paraaminosalicylic acid in tuberculosis; penicillin, streptomycin, and sulfonamides in infections with Gram-negative intestinal bacilli), and (5) a synergistic effect (e. g., penicillin and streptomycin, aureo-

125. Lieberman, D., and Jawetz, E.: Treatment of Chronic Shigella Infection in Children with Oral Polymyxins, Pediatrics **8**:249, 1951.

126. Pulaski, E. J.; Baker, H. J.; Rosenberg, M. L., and Connell, J. F., Jr.: Laboratory and Clinical Studies of Polymyxin B and E, J. Clin. Invest. **28**:1028, 1949.

127. Footnote 122. Swift, P. N.: Treatment of Pertussis with Aerosporin, Lancet **1**:133, 1948.

128. Dowling, H. F.: Established Use of the Antibiotics, Illinois M. J. **100**:192, 1948. Romansky, M. J.: The Synergistic Action and Potential Applications of Antibiotic Combinations, M. Clin. North America **35**:535, 1951. Wellman, W. E.: Combination of Antibiotics in Treatment of Infectious Diseases, Minnesota Med. **34**:537, 1951. Price, C. W.; Randall, W. A.; Welch, H., and Chandler, V. L.: Studies of the Combined Action of Antibiotics and Sulfonamides, Am. J. Pub. Health **39**:340, 1949.

129. Klein, M., and Kimmelman, L. J.: The Correlation Between the Inhibition of Drug Resistance and Synergism in Streptomycin and Penicillin, J. Bact. **54**:363, 1947. Pulaski, E. J.; Voorhees, A. B., Jr., and Seeley, S. F.: Further Experiences with Streptomycin Therapy in Peritonitis, Ann. Surg. **130**:242, 1949.

mycin, or dihydrostreptomycin in peritonitis; aureomycin and bacitracin,[130] neomycin and bacitracin for gastroenteritis in infants [131]; streptomycin, bacitracin, and polymyxin for suppression of the fecal flora [132]).

In vitro studies [133] with combinations of antibiotics have indicated that their effects may be (*a*) synergistic: penicillin and streptomycin on enterococci; penicillin and bacitracin on Gram-positive bacteria; streptomycin, bacitracin, and polymyxin B and other combinations against E. histolytica [134]; streptomycin and bacitracin for intestinal antisepsis [135]; (*b*) additive: aureomycin, chloramphenicol, and dihydrostreptomycin against Ps. aeruginosa and P. vulgaris [136]; (*c*) indifferent, and (*d*) interfering.

Jawetz and his associates [68] have demonstrated that chloramphenicol, as well as aureomycin and terramycin, interferes with the early bactericidal action of penicillin in vitro and in mice against Gram-positive and Gram-negative organisms ordinarily susceptible to penicillin alone. The mechanism of action presumably is some alteration in the bacterial population, decreasing its susceptibility to penicillin. The antagonism occurs only if chloramphenicol is given prior to or simultaneously with penicillin and not if penicillin is administered first. The interference is unilateral, penicillin failing to antagonize the action of the other antibiotics. The effect can be overcome by the use of compounds synergistic with penicillin (streptomycin, bacitracin). Similarly, chloramphenicol, aureomycin, and terramycin interfere in vitro and in vivo with the action of streptomycin. The clinical significance of this phenomenon remains to be established, but the observations suggest caution in the use of multiple antibiotics except when their value is unequivocally established.

The principles of antibiotic therapy in gastrointestinal infections are, of course, the same as those applied to infectious diseases generally. They include accurate clinical and/or bacteriologic diagnosis and adequate doses as rapidly as possible, especially in severe infections. The oral administration of a poorly absorbed anti-

130. Welch, H.; Randall, W. A., and Price, C. W.: Aureotracin: A Combination of Aureomycin and Bacitracin, J. Am. Pharm. A. (Scient. Ed.) **39**:483, 1950.

131. Schaff, B. J.; Spendlove, J. G., and Todd, J. W.: Treatment of Peritonitis with Parenteral Streptomycin and Penicillin, Am. J. Surg. **77**:63, 1949. Kadison, E. R., and Borovsky, M. P.: The Treatment of Infantile Diarrhea with a New Combination of Antibiotics, J. Pediat. **38**:576, 1951.

132. Welch, H.; Randall, W. A., and Price, C. W.: The Effect of Streptomycin-Bacitracin-Polymyxin Combination, Polymyxin B, and Streptomycin with Glucuronolactone on the Intestinal Flora of Man, J. Am. Pharm. A. (Scient. Ed.) **39**:486, 1950.

133. Spicer, S.: Bacteriologic Studies of the Newer Antibiotics: Effect of Combined Drugs on Microorganisms, J. Lab. & Clin. Med. **36**:183, 1950.

134. Gould, M., and Hansen, E. L.: Synergism Between Bacitracin, Polymyxin B, and Streptomycin HCl: In Vitro Tests with Endamoeba Histolytica and Organism t, Federation Proc. **9**:276, 1950. Anderson, H. H., and Anderson, J. V.: Antibiotics Against Amebiasis in Macaques, Am. J. Trop. Med. **30**:193, 1950. Felsenfeld, O.; Kadison, E. R., and Ishihara, S. J.: In Vitro and in Vivo Tests with Newer Antibiotics Against Endamoeba Histolytica, Am. J. Pub. Health **41**:1078, 1951.

135. Finegold, S. M.: Studies on Antibiotics and the Normal Intestinal Flora, Texas Rep. Biol. & Med. **9**:432, 1951.

136. Armstrong, C. W. J., and Lainer, A. E.: Effect of Combinations of Antibiotics on Pseudomonas Aeruginosa and on Proteus Vulgaris in Vitro and in Vivo, J. Lab. & Clin. Med. **37**:584, 1951.

biotic may be inadequate in the treatment of gastrointestinal disease, since the infection often extends deeply into the bowel wall; systemic treatment with a readily absorbed antibiotic probably is more desirable. The quantity of the antibiotic is determined by the type of infection, sensitivity of the infecting organism, and the clinical course. The response should be prompt; if none occurs within 24 to 72 hours, the problem should be reevaluated and a change in antibiotic considered. Severe infections preferably are treated with two or more effective antibiotics, if available, in an effort to control the disease as rapidly as possible. Overtreatment is unwise because of possible toxicity and unnecessary expense. Undertreatment is not desirable because, since antibiotics chiefly exert a bacteriostatic effect, premature cessation of therapy may result in relapse of the infection; therapy probably should be continued until the temperature has remained normal three or five days. Laboratory control is essential in identifying the infecting organism and in measuring its sensitivity to antibiotics. Bacteriologic cultures of material from the nose and throat

TABLE 1.—*Selection of Antibiotics for Adjunct Therapy of Gastrointestinal Diseases*

Disease	Antibiotic
Bacillary dysentery	None superior to sulfadiazine; bacitracin, polymyxin (orally); chloramphenicol, terramycin
Salmonella infections	None outstanding; ? chloramphenicol or terramycin
Typhoid	Chloramphenicol
Amebiasis	Terramycin, aureomycin, bacitracin
Tuberculosis of bowel	Streptomycin with paraaminosalicylic acid
Ulcerative colitis, regional enteritis	None outstanding; many for secondary infection
Suppression of fecal flora	Neomycin, polymyxin (orally), aureomycin, chloramphenicol, terramycin; penicillin and streptomycin (preoperatively and postoperatively)
Peritonitis	Penicillin and streptomycin, aureomycin, terramycin
Biliary tract infections	Same
Hepatitis	? Aureomycin
Weil's disease	Penicillin
Pancreatitis, fibrocystic disease of the pancreas	? Aureomycin
Pseudomonas, proteus infections	Polymyxin B

and of blood are desirable because of the possibility of superinfection. Adjunct medical or surgical treatment, of course, should not be neglected.

Therapeutic failures may be attributed to error in diagnosis, inadequate dosage, delay in treatment, overwhelming infection, localization of the infection in areas inaccessible to the antibiotic, infecting organisms with high natural or acquired resistance to the antibiotic, occurrence of superinfections with other organisms, and the omission of valuable auxiliary medical or surgical measures.

COMMENT

The use of antibiotics in gastroenterology at present has two main objectives: prevention of infection after abdominal surgery and control of those infectious diseases primarily involving the digestive tract.

Poth [111e] has characterized the ideal intestinal antiseptic as possessing a broad antibacterial spectrum, rapid and effective action in small doses, no tendency to induce bacterial resistance, no toxic effects, no tendency toward production of gastrointestinal symptoms, and no tendency to retard healing. None of the available antibiotics completely satisfies all these criteria, in our opinion. Nor has it been possible to completely sterilize the intestine, should that effect be desirable. On the

TABLE 2.—*Certain Undesirable Effects of Antibiotic Therapy*

Reaction	Penicillin	Streptomycin; Dihydrostreptomycin	Aureomycin	Chloramphenicol	Terramycin	Neomycin IM, IV	Bacitracin IM, IV	Polymyxins IM, IV
Hypersensitivity (fever, skin eruptions, asthma, anaphylaxis)	Common	Common	Infrequent at present			.....	0	Common
Gastrointestinal (nausea, vomiting, diarrhea, glossitis, stomatitis, esophagitis, proctitis)	0	0	Common			Occasional	Occasional	0
Neurologic	0	Tinnitus; vertigo; deafness	Neuritis (rare)	Vertigo (rare)	0	Deafness; vertigo	0	Weakness; paresthesia; ataxia; nystagmus; diplopia
Hematologic	0	Eosinophilia; anemia (rare)	Neutropenia; anemia (rare)	Neutropenia; aplastic anemia	0	0	0	0
Renal	0	0	0	0	0		Common	
Superinfection			Occurs				Infrequent at present	
Bacterial resistance	Occurs	Common, rapid	Infrequent at present				May occur	

other hand, most antibiotics, with the exception of penicillin, modify the fecal flora in some degree, and their use has reduced dramatically the incidence of postoperative infection and the mortality from peritonitis.[137] Aureomycin, terramycin, penicillin, and streptomycin, or neomycin, may be preferred, but, regardless of the antibiotic used, suppression of the fecal flora is temporary.[138] Suppression of the flora is even more difficult in the presence of perforated intestinal lesions associated with abscess cavities, intestinal fistulas, and obstruction, probably because they interfere with contact between antibiotic and micro-organism. The development of a fecal flora resistant to penicillin, streptomycin, aureomycin, and chloramphenicol after prolonged administration of these compounds has been demonstrated in man[49d]; the development of bacterial resistance to the newer antimicrobial agents also may be anticipated. These observations emphasize the importance of proper "timing" ir antibiotic therapy; present data suggest the administration of antibiotics for three or five days before operation and for seven to ten days afterward. The availability of antibiotics does not, of course, lessen the importance of skillful technique in preventing contamination of the peritoneal cavity at the time of operation, adequate replacement of electrolytes and fluids, and the administration of blood.

In addition to the alteration in fecal flora, antibiotics also modify the flora of the nasopharynx. The suppression or elimination of one bacterial species may permit the growth and enhance the virulence of other organisms, originally present in small numbers, usually regarded as not pathogenic, and insensitive to the antibiotic being used.[139] The infection may result from a disturbance of the equilibrium maintained by the bacterial antagonisms within the normal flora. Superinfection with hemolytic Staphylococcus pyogenes var. aureus,[139c] Bacillus pyocyaneous (Ps. aeruginosa),[139d] Esch. coli, and A. aeruginosa[139d] has been described during penicillin therapy;

137. (*a*) Altemeier, W. A.: The Present Status of Antibiotic and Chemotherapeutic Agents in Surgery, Pennsylvania M. J. **53**:1257, 1950. (*b*) Riddell, M. I.: Review of Literature on Preoperative Prophylaxis of Bowel with Antibacterial Agents, Am. J. M. Sc. **223**:301, 1952.

138. Bierman, H. R., and Jawetz, E.: The Effect of Prolonged Administration of Antibiotics on Human Fecal Flora, J. Lab. & Clin. Med. **37**:394, 1951.

139. (*a*) Finland and Wells.[1d] (*b*) Finland.[1e] (*c*) Weinstein, L.: The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin, Am. J. M. Sc. **214**:56, 1947. (*d*) Appelbaum, E., and Leff, W. A.: Occurrence of Superinfection During Antibiotic Therapy, J. A. M. A. **138**:119, 1948. (*e*) Astler, V. B., and Morgan, H. R.: Some Biologic Complications of the Prophylactic and Therapeutic Use of Antibiotics, Univ. Michigan M. Bull. **16**:127, 1950. (*f*) Cross, W. G.: Oral Reactions to Penicillin, Brit. M. J. **1**:171, 1949. (*g*) Hewitt, W. L., and Williams, B., Jr.: Chloromycetin (Chloramphenicol) in the Treatment of Infections, New England J. Med. **242**:119, 1950. (*h*) Harris, H. J.: Aureomycin and Chloramphenicol in Brucellosis with Special Reference to Side Effects, J. A. M. A. **142**:161, 1950. (*i*) Williams, B., Jr.: Oral and Pharyngeal Complications of Chloramphenicol (Chloromycetin) Therapy, Am. Pract. & Digest Treat. **1**:897, 1950. (*j*) Geiger, A. J.; Wenner, H. A.; Axilrod, H. D., and Durlandes, S. H.: Mycotic Endocarditis and Meningitis, Yale J. Biol. & Med. **18**:259, 1945. (*k*) Meads, M.; Rowe, W. P., and Haslam, N. M.: Alterations in Bacterial Flora of Throat During Oral Therapy with Aureomycin, A. M. A. Arch. Int. Med. **87**:533, 1951. (*l*) Woods, J. W.; Manning, I. H., Jr., and Patterson, C. W.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**:207, 1951. (*m*) Kligman, A. M.: Are Fungus Infections Increasing as a Result of Antibiotic Therapy? ibid. **149**:979, 1952. (*n*) Yow, E. M.: Development of Proteus and Pseudomonas Infections During Antibiotic Therapy, ibid. **149**:1184, 1952.

staphylococcic glossitis and pharyngitis during the use of streptomycin; staphylococcic diarrhea during the use of terramycin,[1d,e] and M. candida infections of the mouth, vagina, and rectum during treatment with aureomycin, chloramphenicol, and terramycin.[1891] Superinfection with Pseudomonas and especially Proteus organisms may be difficult to control. The complication is more likely to occur in the very young, the aged, or the debilitated patient. The incidence of superinfection probably will increase with the more extensive use of antibiotics.

In contrast to the established value of antibiotics in abdominal surgery and in the management of peritonitis, the role of antibiotics in the treatment of other gastrointestinal infections seems less dramatic. In vitro sensitivity tests serve only as a first approximation and do not necessarily predict the clinical response.[1e'] Observations on animals, such as mice, rabbits, and dogs, likewise may not be reproducible in man. Evaluation of the clinical response may be difficult. Favorable reports in many instances are based upon the limited observation of small groups of cases; the findings often are equivocal. Salmonella and Shigella infections frequently are self-limited and subside rapidly without specific therapy. The administration of antibiotics in such circumstances may be fortuitous rather than curative. In bacillary dysentery none of the currently available antibiotics excels sulfadiazine or other sulfonamides, except in the presence of sulfonamide-resistant bacteria. The susceptibility of different strains of organisms seems to vary greatly and is modified further by exposure to antibiotics. The action of antibiotics in diseases such as Salmonella and Shigella infections and typhoid seems to be primarily bacteriostatic or suppressive, and ultimate recovery is dependent upon the development of immunity in the host. Pratt and Dufrenoy [1a'] suggest that antibiotics, by rapidly suppressing invading organisms, may remove the stimulus for antibody formation before the normal defense mechanisms of the body are completely mobilized. Resistance to reinfection consequently might be weaker in a patient given antibiotics early in the course of the disease, in contrast to the patient receiving treatment after the infection had been in progress for several days. These authors cite recent experimental and clinical evidence compatible with this view.[140]

In ulcerative colitis and regional enteritis, antibiotics appear to be of value chiefly in the control of secondary infection, such as abscess formation and peritonitis.[141] Their administration frequently is based upon the possibility of an undetected bacterial infection with organisms susceptible to the antibiotic. Improvement may occur, but relapses are frequent, and repeated antibiotic therapy is not consistently effective. The role of the recognizable intestinal bacteria in ulcerative colitis is not clear; decreasing the fecal flora seems to be helpful primarily in reducing the possibility of secondary infection. The bacterial content of the feces in ulcerative colitis is higher than normal; in one study the total bacterial count was increased eighty-five-

140. Anigstein, L.; Whitney, D. M., and Beninson, J.: Aureomycin: Protective Effect in Experimental Rocky Mountain Spotted Fever and Typhus with Particular Reference to Intermittent Therapy, Texas Rep. Biol. & Med. **7**:96, 1949; cited by Pratt and Dufrenoy.[1a'] Montestruc, E.; Blache, R., and Vildrin, A.: Chloromycetin and Typhoid Serology: Prophylactic Value of Chloramphenicol Cure, Bull. Soc. path. exot. **43**:135, 1950; cited by Pratt and Dufrenoy.[1a']

141. Block M., and Pollard, H. M.: Chemotherapy and Antibiotics in Chronic Ulcerative Colitis, Gastroenterology **10**:46, 1948.

fold and the coliform organisms were increased to 50 times more than normal.[142] However, modification of the fecal flora is not necessarily correlated with the clinical response. The etiological significance of various intestinal pathogens in ulcerative colitis and regional enteritis similarly is not clear. On the other hand, the possible production of lytic enzymes by the bacterial flora merits further study in relation to the pathogenesis of ulcerative colitis.

The beneficial effect of antibiotics in intestinal amebiasis appears more definite. The mechanism of action involves primarily suppression of the associated bacterial flora and, to a smaller degree, direct amebicidal effect. Nevertheless, more data are needed concerning the effectiveness of antibiotic therapy in amebiasis. The evidence to date indicates that antibiotics are of little or no value in the management of amebic infections of the liver. Perhaps the true value of antibiotics in amebiasis will be as highly useful adjuncts to treatment with standard amebicidal compounds.

The value of antibiotic therapy in hepatic disease is uncertain. Those antibiotics excreted in high concentrations in the bile appear to be useful in the management of infections of the biliary tract. The favorable responses noted occasionally in patients with hepatitis and/or hepatic coma are provocative and require further investigation. However, the evidence is by no means conclusive. In so serious an illness any therapeutic effort seems justifiable, but better-controlled studies are necessary.

The clinical value of antibiotics in gastroenterology, as in other fields, must be assessed not only with reference to therapeutic result but also in relation to toxic effects, sensitization of the patient to the antibiotic, the cultivation of bacteria resistant to the antibiotic, and the implication of these developments for the treatment of serious infection in the future. Miller [18] recently has commented upon the increasing prevalence of infections caused by bacteria resistant to present antibiotic drugs. More information is needed concerning the chemical and metabolic effects of antibiotics in man, optimal dosage, multiple antibiotic therapy, and bacterial resistance.[143] Despite these limitations in knowledge, antibiotics are definitely helpful in the management of certain gastrointestinal diseases when carefully administered in conjunction with other established methods of treatment (Table 1). They should not be prescribed indiscriminately, since per se they may cause gastrointestinal discomfort and diarrhea. New and possibly more effective antibiotics will be forthcoming. Their value will continue to be determined largely by accurate diagnosis and sound clinical judgment.

142. Seneca, H., and Henderson, E.: Normal Intestinal Bacteria in Ulcerative Colitis, Gastroenterology **15**:34, 1950.

143. Jawetz, E., and Marshall, M. S.: The Role of the Laboratory in Antibiotic Therapy, J. Pediat. **37**:545, 1950.

Case Reports

PERNICIOUS ANEMIA OCCURRING SIMULTANEOUSLY IN IDENTICAL NEGRO TWINS

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THE SIMULTANEOUS occurrence of a disease process in identical twins is of interest to students of medicine and genetics. The familial incidence of pernicious anemia and achlorhydria has been well recognized in Europe and in this country.[1] Though the occurrence of pernicious anemia has been reported in identical male and female Caucasian twins,[2] we could find no instance of its report in Negro twins or of its simultaneous occurrence in any one pair of twins. Brief reports with less confirmatory evidence of pernicious anemia in twins have been made by other authors.[3]

The following is a report of pernicious anemia occurring simultaneously in identical Negro female twins.

REPORT OF CASES

CASE 1.—The first of the twins, J. M. S., a 72-year-old Negro woman, was admitted to the George Washington University Medical Division of Gallinger Municipal Hospital on Oct. 24, 1950, and was discharged on Dec. 1, 1950. The onset of her present illness was gradual, and she was forced to stop work as a cook about four months preceding her admission because of anorexia, nausea, vomiting, and progressive weakness. A local physician prescribed digitalis and a tonic, but she failed to improve and became bedridden prior to admission. She had also noted vertigo, dyspnea on exertion, intermittent diarrhea, and weight loss of 10 lb. (4.5 kg.) during the preceding 10 months. She denied hematemesis, melena, dysphagia, hemoptysis, sensory changes, or painful tongue. Her nutrition before the present illness was apparently adequate.

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1. (*a*) Meulengracht, E.: The Hereditary Factor in Pernicious Anemia, Am. J. M. Sc. **169**:177 (Feb.) 1925. (*b*) Schauman, O.: Über das familiäre Auftreten der perniciösen Anämie, Finska läk.-sällsk. handl. **60**:526, 1919. (*c*) Gilford, H.: Addison's Anemia, Lancet **1**:64-66 (Jan. 13) 1923. (*d*) Levine, S. A., and Ladd, W. S.: Pernicious Anemia, Bull. Johns Hopkins Hosp. **32**:254 (Aug.) 1921. (*e*) Hurst, A. F.: Clinical Importance of Achlorhydria, Brit. M. J. **2**:665 (Oct. 13) 1934. (*f*) Castle, W. M., and Minot, G. R.: Pathological Physiology and Clinical Description of the Anemias, New York, Oxford University Press, 1936, pp. 630. (*g*) Kaufmann, O., and Thiessen, K.: Zur Erbbiologie der perniciösen Anämie, Ztschr. klin. Med. **136**:474, 1939. (*h*) Askey, J. M.: Prevention of Pernicious Anemia: Recognition of Latent Stage in Relatives, Ann. Int. Med. **14**:593 (Oct.) 1940. (*i*) Stamos, H. F.: Heredity in Pernicious Anemia, Am. J. M. Sc. **200**:586 (Nov.) 1940. (*j*) Schemm, F. R.: Pernicious Anemia Family, ibid. **199**:167 (Feb.) 1940.

2. (*a*) Kaufmann and Thiessen.[1g] (*b*) Frank, H.: Erblichkeit der Anaemia perniciosa und Beobachtung an eineiigen Zwillingen, Deutsches Arch. klin. Med. **175**:96, 1933. (*c*) Schwartz, G. A., and Todd, J. C.: Subacute Combined Degeneration in Identical Twins, Am. J. M. Sc. **214**:94 (July) 1947.

3. Hurst.[1e] Stamos.[1i] Strandell, B.: Pernicious Anemia: A Study of 117 Cases, Acta med. scandinav., Supp. 40, p. 1, 1931. Weitz, W.: Die Vererbung innerer Krankheiten, Stuttgart, Ferdinand Enke, 1936.

The past history was noncontributory.

Family history revealed that her mother, a mulatto, died in 1929 at the age of 72 with signs and symptoms similar to those of the patient's present illness. She had no knowledge of her grandparents. Her father died at the age of 74 from unknown causes, and the history of six other siblings was noncontributory. She further volunteered the information that her twin sister was ill at home with the "same trouble."

Admission Physical Examination.—The patient was a cooperative, elderly Negro woman, moderately light-skinned, chronically ill, apathetic in expression, and sluggish in responses. Her height was 5 ft. 2 in. (157.5 cm.) and her weight 130 lb. (59 kg.). The temperature was 98 F., pulse rate 78, respiration rate 20, and blood pressure 122/60. The skin of the face and trunk was covered with multiple, small, dark nevi. The nail beds and mucosal surfaces were extremely pale. The tongue was smooth along the edges, and the papillae were low and atrophic over the remainder. Early bilateral cataract formation was present. A Grade 2 systolic murmur was heard over the aortic area. The liver was palpable 4 cm. below the right costal margin. With the exception of a small urethral caruncle, the pelvic and rectal examinations revealed no abnormality. A doubtful Romberg sign, loss of fine position sense in the toes, loss of vibration sense below the iliac crests, and diminished vibration sense in the upper extremities were noted.

Laboratory Data.—The blood studies on admission showed 4.4 gm. of hemoglobin per 100 cc., 930,000 red blood cells, a hematocrit reading of 16%, mean corpuscular volume of 170 cu. μ, mean corpuscular hemoglobin of 47.5 micromicrograms, mean corpuscular hemoglobin concentration of 27.5%. Reticulocytes were 2.4%. The icterus index was 12. White blood cells numbered 5,000, with 65 polymorphonuclear cells, 1 band cell, 31 lymphocytes, 2 monocytes, and 1 eosinophile on differential count, with marked anisocytosis and poikilocytosis. The thrombocyte (platelet) count was 58,590. Urinalysis revealed a specific gravity of 1.017, a trace reaction for albumin, negative reactions for sugar and acetone, 2 or 3 white blood cells and 1 or 2 red blood cells per high-power field on microscopic study. Total protein was 7.21 gm., with 4.40 gm. of albumin and 2.81 gm. of globulin. The prothrombin time was 90% of normal. The Kahn test gave a negative reaction. Gastric analysis revealed achlorhydria following histamine stimulation. Serum phosphorus was 4 mg. and serum calcium 10.3 mg. per 100 cc. Alkaline phosphatase was 3.08 units. Stool examination for occult blood, ova, and parasites revealed none. Bone marrow smears from the sternum revealed 35% megaloblasts and many giant metamyelocytes consistent with a diagnosis of pernicious anemia in relapse. A complete gastrointestinal series, chest roentgenogram, and electrocardiogram were within normal limits.

Hospital Course.—Oral therapy was started with an experimental preparation of 10 γ of vitamin B_{12} daily along with 1,000 mg. of stomach concentrate for 29 days.[4] The reticulocyte response was submaximal at 6.2% on the 9th day, and a peak response of 14.4% was reached on the 20th day. One blood transfusion of 500 cc. was given shortly after admission. The clinical response to therapy was good, anorexia disappeared, and the patient voluntarily became ambulatory about the 10th hospital day. The hematocrit reading progressed steadily upward to 30% at the time of discharge; the liver was no longer palpable, position sense in the lower extremities was approaching normal, but the vibration sense remained unchanged. The heart murmur had diminished greatly in intensity. Parenteral vitamin B_{12} therapy was prescribed, and she was discharged. On visits to the hematology clinic she continued to improve, and three months from the time of her initial hospitalization the red blood cell count was 4,120,000 and the hematocrit reading 39%. She is again doing her housework and feels very well; after one year, her erythrocyte count is 4,310,000 and the hematocrit reading is 41%.

CASE 2.—M. M. O. was admitted to the George Washington University service of Gallinger Municipal Hospital on Nov. 3, 1950, and was discharged on Dec. 1, 1950. Her admission was prompted by her sister's report that her twin was sick at home with similar symptoms. M. M. O. became ill about six weeks prior to admission, when she noted dyspnea, anorexia, nausea, vomiting, weakness, and stiffness and pain in her fingers. She gave a history of several attacks of paroxysmal nocturnal dyspnea, for which a private physician had been treating her with digitalis. Vertigo had also been present, with three episodes of syncope. She denied hematemesis, melena, dysphagia, hemoptysis, and painful tongue. Numbness and tingling in her finger and toes were present and troublesome.

4. The stomach concentrate was obtained through courtesy of Dr. Kenneth Thompson, Organon, Inc., Orange, N. J.

The past history was noncontributory. The family history is given above.

Physical Examination.—On admission to the hospital the physical examination revealed an elderly Negro woman, moderately light-skinned, appearing chronically ill and lying comfortably flat in bed. She continually rubbed her hands and fingers together. She was 5 ft. 2 in. (157.5 cm.) tall and weighed 135 lb. (61.2 kg.). The temperature was 100 F., pulse rate 78, respiration rate 20, and blood pressure 120/60. Numerous dark, small, flat-topped nevi were present over the face and trunk. The nail beds and mucosal surfaces were very pale. The tongue was smooth along the edges, with a flattening of the papillae over the remainder. Early cataract formation was present bilaterally. A Grade 2 systolic murmur was heard over the apex and over the aortic area. The knee jerks were 1+; ankle jerks were absent; position sense was absent in the lower extremities, and vibration sense was absent at and below the iliac crests. The Romberg sign was not elicited. Results of the remainder of the physical examination were essentially normal.

Laboratory Data.—The blood studies on admission disclosed 4.5 gm. of hemoglobin per 100 cc., 1,240,000 red blood cells, a hematocrit reading of 15%, mean corpuscular volume of 121 cu. μ, mean corpuscular hemoglobin of 36.5 micromicrograms, and mean corpuscular hemoglobin concentration of 30%. Reticulocytes were 0.1% and white blood cells 5,650, and 66 polymorphonuclear cells, 1 band cell, 27 lymphocytes, 3 eosinophiles, and 2 nucleated red cells seen on differential counts. Anisocytosis and poikilocytosis were present. Thrombocytes numbered 131,020. The icterus index was 15. Urinalysis revealed cloudy-amber color, an acid reaction, a specific gravity of 1.011, and negative reaction for albumin, sugar, and acetone. Microscopic examination showed 5 to 10 epithelial cells per high-power field. Serum phosphorus was 2.5 mg. and serum cholesterol 147 mg. per 100 cc., with 83.3% esters. Alkaline phosphatase was 1.14 units. The Kahn reaction was negative. Total protein was 6.20 gm., with 3.77 gm. of albumin and 2.43 gm. of globulin. Cephalin flocculation was 1+ after 48 hours. Gastric analysis following histamine stimulation showed achlorhydria. A complete gastrointestinal series was normal. A chest roentgenogram showed mild cardiomegaly in the transverse and long diameters. Bone marrow smears from the sternum revealed 48% megaloblasts and bizarre giant metamyelocytes consistent with a diagnosis of pernicious anemia. Stool examinations were negative for occult blood, ova, and parasites. The electrocardiogram was normal.

Hospital Course.—The patient was transfused with 500 cc. of whole blood after admission, and oral administration was started of an experimental preparation of vitamin B_{12} and pyloric concentrate; however, because of extreme weakness, it was decided to change to administration of 30 γ of vitamin B_{12} parenterally daily. The reticulocyte response was 27.5% by the fourth day of therapy, and her hematocrit reading and erythrocyte count began a slow but steady rise. The clinical response to therapy was excellent, and she became ambulatory about two weeks following admission. The pain and tingling sensation in her fingers and hands continued unabated and were only slightly diminished by the time of discharge. The knee and ankle reflexes returned to normal, as did the vibration sense above the malleoli; the position sense, however, remained impaired. The cardiac murmurs were diminished in intensity but still present. The patient has been followed in the hematology clinic since discharge, and improvement has continued. Four months following her discharge from the hospital her erythrocyte count was 4,230,000 and her hematocrit reading was 39%. A year later the hematocrit reading had risen to 42%.

COMMENT

This case report involves identical Negro female twins, 72 years of age. They were born in South Carolina and resided there until the age of 48, when they moved to the District of Columbia. The twins have lived with, or near, each other all their lives. As children they had measles, mumps, chickenpox, whooping cough, and typhoid at the same time and had no complications with these diseases. Since moving to the District of Columbia, they have been living in the same household and eating the same food, although J. M. S. cooked in another household and consumed two-thirds of her meals in that household, away from M. M. O. It was interesting to note that the husband of one of the twins (aged 92) and an elder sister (aged 85) are living in the same home and eating from the same kitchen. Careful hemato-

logical examinations of those persons and of one other member of the household revealed no evidence of anemia. The onset of the symptoms of pernicious anemia in one of the twins occurred within weeks of onset in the other, which seems to be more than coincidental. Since neither of the twins avoided proteins, it is felt that nutritional deficiency did not enter into the causation. Since their discharge from the hospital they have continued on the same diet and have remained well.

The available evidence points to the monozygocity of the twins. They both maintain that they have been considered "identical" all their lives. No record is available of the presence of a single or double chorion at birth. In physical appearance they have the same features and stature. Their blood types are similar, being Type O, Rh-positive (cDe/cDe). It has been stated in a previous publication [2c] that the fingerprints of monozygotic twins are similar in appearance, although not necessarily identical. The Federal Bureau of Investigation classification of the

Signs of pernicious anemia in identical female Negro twins.

fingerprints of J. M. S. was 31-IOO-22/28-OOI-16 and of M. M. O. 31-Moo-17/28-OII-23. This is a gross similarity. An FBI representative also informed us, however, that the Bureau has on file a large number of prints from identical twins that are not even grossly similar, and that in their opinion this particular method of establishing monozygocity is not reliable.

SUMMARY

A report is presented of pernicious anemia occurring simultaneously in 72-year-old female Negro twins.

Discussion of diagnosis and treatment in the patients and one-year follow-up observations are presented. The genetic implications are stressed.

It is believed that this is the first instance reported of pernicious anemia in Negro twins, as well as the first instance reported of pernicious anemia occurring simultaneously in twins of any race.

REPEATED BOUTS OF RENAL PAPILLARY NECROSIS DIAGNOSED BY EXAMINATION OF VOIDED TISSUE

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ATLANTA

ACUTE necrosis of the renal papillae occurs in diabetic patients with acute pyelonephritis and in nondiabetic patients with urinary tract obstruction.[1] In a few patients, papillary necrosis has been encountered in the absence of diabetes and urinary tract obstruction.[2] However, acute pyelonephritis is a consistent finding.

In four instances, the occurrence of papillary necrosis has been recognized during life by histological examination of tissue passed in the urine.[3] Alken,[4] in Germany (1938), reported a case of papillary necrosis in a 50-year-old woman with painless hematuria. There was decreased function of the left kidney; Escherichia coli was found in the urine, and pyelography demonstrated a defect in the left upper calyx. Six months later, she returned with renal colic on the left. A portion of tissue was passed in the urine, and the diagnosis was made histologically. Recently, Knutsen and co-workers observed a patient for whom the diagnosis was established by histological examination of a necrotic papilla removed during cystoscopy.[3a]

Repeated episodes of papillary necrosis verified by histological examination of tissue passed in the urine and by autopsy occurred in the patient reported on here.

REPORT OF A CASE

Final Hospital Admission.—A 24-year-old white male student was admitted to Grady Memorial Hospital, Sept. 3, 1951, because of flank pain and high fever.

He was known to have had moderately severe, poorly controlled diabetes for 11 years, with evidence of marked retinopathy and neuropathy. There had been no history of hypertension.

In May, 1951, while in the ophthalmology service for treatment of a cataract, he was found to have a temperature elevation to 101 F. His urine contained many white blood cells and bacteria, and a urine culture grew paracolon bacillus and Aerobacter aerogenes. The blood urea

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1. Robbins, E. D., and Angrist, A.: Necrosis of Renal Papillae, Ann. Int. Med. **31**:773 (Nov.) 1949.

2. Sheehan, H. L.: Medullary Necrosis of the Kidneys, Lancet **2**:187 (July 24) 1937.

3. (*a*) Knutsen, A.; Jennings, E. R.; Brines, O. A., and Axelrod, A.: Renal Papillary Necrosis, Am. J. Clin. Path. **22**:327 (April) 1952. (*b*) Mandel, E. E.: Renal Medullary Necrosis, Am. J. Med. **13**:322 (Sept.) 1952.

4. Alken, C. E.: Die Papillennekrose, Ztschr. Urol. **32**:433, 1938; cited by Edmundson, H. A.; Martin, H. E., and Evans, N. G.: Necrosis of Renal Papillae and Acute Pyelonephritis in Diabetes Mellitus, Arch. Int. Med. **79**:148 (Feb.) 1947.

nitrogen was 22 mg. per 100 cc., and the hemoglobin concentration was 10 gm. per 100 cc. After sulfadiazine therapy, the fever subsided, and the patient was discharged to the outpatient department.

He was seen frequently in the urology clinic, and pyuria with bacilluria persisted in spite of continued sulfadiazine therapy. Six weeks before admission, flank tenderness and low-grade fever were noted. On July 26, five weeks before admission, a retrograde pyelogram demonstrated abnormalities which suggested a defect in the left lower calyx.

On Aug. 2, four weeks before admission, he experienced sudden severe, cramping pain in the right flank which persisted for several minutes. One hour after the onset of pain, he passed two oblong pieces of tissue in his urine. There was no further exacerbation of symptoms at this time.

On Sept. 2, the day before admission, he again had transient cramping pain in the left flank and voided additional pieces of tissue. Two hours later, he had a shaking chill, became very hot, and went to bed.

On the day of admission he was found comatose in bed. Urinary and fecal incontinence and a cool moist skin were noted. In the emergency clinic he received two intravenous infusions of dextrose and water and promptly regained consciousness. After the second infusion, he had a shaking chill and was admitted to the hospital.

On admission his temperature was 104 F. The pulse rate was 124. The blood pressure was 130/110 supine and 60/40 standing. The skin was pale and hot. Bilateral lenticular opacities were present. The fundi of the eyes revealed narrow irregular arterioles, flame-shaped hemorrhages, and numerous "capillary aneurysms." The liver edge was palpated 2 cm. below the right costal margin. The lower pole of the left kidney was palpable and tender. There was moderate bilateral flank tenderness. Knee and ankle jerks were absent, and there was impaired sensation to pain, vibration, and light touch in the lower extremities.

Significant laboratory findings on admission were marked pyuria, mild hematuria, moderate anemia, and blood urea nitrogen of 49 mg. per 100 cc. A urine culture grew a paracolon bacillus and Pseudomonas aeruginosa. These organisms were sensitive, in vitro, to chloramphenicol (chloromycetin®), but resistant to aureomycin, streptomycin, and sulfadiazine.

Twenty-four hours after oral chloramphenicol therapy was begun, the temperature rapidly fell to normal, and the patient's general condition improved considerably. However, the diabetes was controlled with some difficulty, and a second urine culture grew a Proteus organism and Ps. aeruginosa.

On the 27th hospital day, the patient experienced intermittent, transient, cramping pain in the right flank, followed by the passage of grossly bloody urine containing fragments of tissue. The temperature rose to 103 F., and the dosage of chloramphenicol was increased. Subsequently, the temperature gradually fell to normal, and the patient objectively improved. However, the pyuria and bacilluria of Proteus and Pseudomonas organisms remained. The organisms were resistant to high concentrations of sufisoxazole (gantrisin®), sulfadiazine, streptomycin, aureomycin, terramycin, chloramphenicol, and polymyxin.

Between the 40th and 51st hospital days, generalized edema was noted, and there was a gradual marked increase in weight.

On the 49th hospital day the patient voided grossly bloody urine containing two additional pieces of tissue. There was no pain. Several hours later, several shaking chills occurred, followed by temperature rises to 102 F. Subsequently, the temperature again gradually returned to normal, and the edema slowly disappeared. Despite persisting pyuria and bacilluria, the patient became asymptomatic and was discharged from the hospital.

During hospitalization, the patient's urine remained dilute, the specific gravities ranging from 1.002 to 1.010. His weight varied considerably and tended to increase somewhat during the week prior to the discharge of papillae. One to two weeks preceding the final episode of colic, his weight increased from 130 to 142 lb. (59 to 64.4 kg.). Five days following the passage of papillae his weight returned to 130 lb. The level of blood urea nitrogen ranged around 36 mg. per 100 cc. but tended to rise to about 80 mg. per 100 cc. with the episodes of renal colic. However, at the time of his discharge from the hospital, it was 20 mg. per 100 cc.

Because of the inconstant food intake, the patient's diabetes was difficult to control. Fasting blood sugar levels varied from 24 mg. per 100 cc. on admission to 757 mg. during the febrile episodes. Treatment consisted of a 2,200-calorie diabetic diet and 30 units of protamine zinc insulin daily. Urinary sugar levels correlated well with blood sugar values. The urine remained free of acetone throughout the hospital course, and the blood carbon-dioxide-combining power was not appreciably altered.

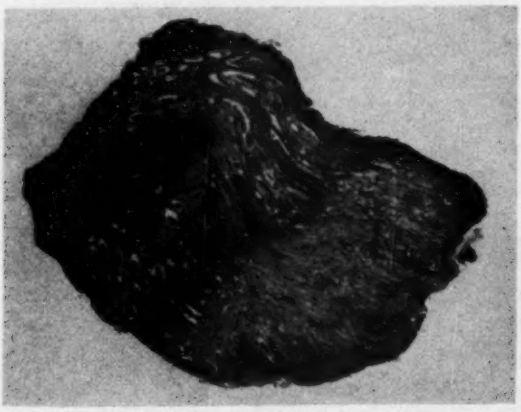

Fig. 1.—Fragment of necrotic renal papilla passed in urine. Hematoxylin and phloxine stain; × 10.

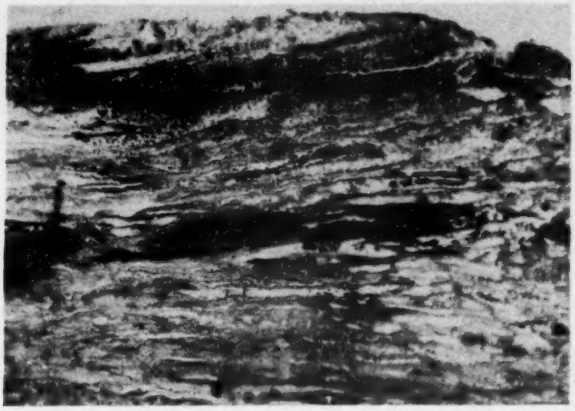

Fig. 2.—Same fragment of necrotic papilla as in Figure 1 at higher magnification. Ghost-like contours of the tubules can be recognized. Dark-staining materials are polymorphonuclear leucocytes and masses of bacteria. Hematoxylin and phloxine stain; × 95.

After his discharge from the hospital, the patient was followed at monthly intervals in the diabetic clinic. When last seen, two months after discharge, he was asymptomatic and afebrile, with a blood urea nitrogen of 18 mg. per 100 cc.

Ten weeks following discharge, he had a severe insulin reaction and died en route to the hospital.

Morphological Findings.—Surgical Specimens: On four occasions in three and one-half months, tissue fragments were passed in the urine. The first specimen, obtained one month before admission, consisted of two soft, smooth, brown, somewhat cone-shaped pieces of tissue, measuring 15 mm. in length and 5 mm. in largest diameter. Histological examination revealed necrotic renal papillae surrounded by a rim of polymorphonuclear leucocytes (Figs. 1 and 2). Many tubules contained cellular debris and masses of bacteria.

The second and fourth specimens were also examined histologically; the second specimen was similar to the first, but the fourth specimen showed only blood clot with numerous bacterial colonies.

Autopsy Observations: Necropsy was performed approximately 24 hours after death and 16 hours after embalming. Permission to examine the head and neck was not granted.

Gross findings: The gross appearance of the tissues was obscured by embalming.

Both the left kidney (220 gm.) and the right kidney (250 gm.) revealed smooth outer surfaces, with scattered 4- to 7-mm. depressed stellate scars to which the capsule and perirenal fat were adherent. The cut surfaces showed poor demarcation of the cortex and medulla, with indistinct cortical striations and numerous ill-defined streaky areas of reddish-yellow discoloration. The

Fig. 3.—Cut surfaces of one kidney showing loss of renal papillae. Note area of pyelonephritis at lower pole (left).

tips of all papillae were replaced by crater-like defects (Fig. 3). Two of the major calyces in the lower pole of the left kidney contained soft grayish-yellow masses resembling necrotic papillae. The calyces and pelves were lined by grayish-yellow mucosa containing a few 1- to 2-mm. firm nodules. The renal vessels were not remarkable. Both ureters were patent and of normal caliber. Their mucosa was similar to that of the calyces and pelves. The bladder contained 100 cc. of cloudy yellow fluid. Its wall appeared somewhat thickened, and the mucosa was studded with yellow 3- to 4-mm. nodules. The ureteral and urethral openings were patent.

Additional gross findings were splenomegaly (weight of spleen, 220 gm.), hepatomegaly (weight of liver, 2,030 gm.), a few fibrous peritoneal adhesions, and two minute sessile polypi, one in the sigmoid colon, the other in the rectum. The heart was of normal shape and weight (370 gm.; normal weight, 332 $\pm$ 40 gm.). The pancreas weighed 75 gm. and was of normal shape and consistency.

Histological observations: The kidneys showed extensive streaky areas of acute as well as chronic inflammatory cell infiltration involving both cortex and medulla. Polymorphonuclear leucocytes predominated in the areas of acute inflammation, in which occasional microabscesses were encountered. In the areas of older inflammation, lymphocytes and plasma cells prevailed, and there was considerable scarring. The inflammatory process had produced extensive destruc-

tion of both glomeruli and tubules. The arterioles throughout displayed considerable onion-peel-like thickening of their walls.

The papillae were replaced by scar tissue which in most instances was of dense hyaline character (Fig. 4). In a few areas more recent granulation tissue was found with a subsiding acute inflammation. Recent necrosis was not encountered. In every instance the calyceal epithelium was completely, or at least partially, covering the denuded areas (Fig. 5). Frequently,

Fig. 4.—Kidney. Renal papilla is replaced by a deep crater-like defect. Hematoxylin and phloxine stain; × 75.

Fig. 5.—Kidney. Fundus of crater shown in Figure 3. Newly regenerated epithelium of the renal pelvis covers scar tissue. Hematoxylin and phloxine stain; × 150.

this epithelium was seen to extend for a short distance into the collecting ducts of the pyramids, apparently reestablishing their continuity. Within the scar tissue some small cysts were found, lined by flattened epithelium. These appeared to represent obstructed collecting ducts.

The masses found in two calyces of the left kidney consisted of necrotic renal papillae surrounded by polymorphonuclear leucocytes.

The pancreatic acini and islets were not remarkable.

In addition, some glycogen infiltration of the liver, lymphoid depletion of the lymph nodes and spleen, slight secondary hyperplasia of the bone marrow, and two adenomatous polypi of the large intestine, were observed.

Anatomical Diagnoses.—Anatomical diagnoses were as follows: marked acute and chronic pyelonephritis with extensive old and recent necrosis of renal papillae; marked follicular cystitis, ureteritis, and pyelitis; diabetes mellitus (clinical); glycogen infiltration of the liver; generalized arteriosclerosis; lymphoid depletion of the spleen and lymph nodes; adenomatous polypi (two) in sigmoid colon and rectum, and peritoneal adhesions, fibrous.

COMMENT

The clinical course and morphological observations in our patient are those of typical papillary necrosis involving both kidneys and occurring in association with diabetes and acute and chronic pyelonephritis. The unusual aspects of this case were the repeated episodes of papillary necrosis and sequestration, followed by the passage of necrotic papillae in the urine. The observations made on this patient suggest that, while papillary necrosis in itself does not appear to produce recognizable symptoms, the sequestration and passage of the necrotic material were associated with pain, hematuria, chills, and elevation of blood urea nitrogen. The patient himself called attention to the passage of tissue in the urine. Histological examination of the material showed readily recognizable necrotic renal medullary tissue and verified the repeated episodes of papillary necrosis. At autopsy, advanced repair of the papillary areas was demonstrated. Furthermore, the clinical course of this patient, extending for at least five months, indicates that the repair was adequate to permit recovery of renal function.

Papillary necrosis occurs not infrequently. In a recent autopsy study [5] on diabetic patients, acute pyelonephritis was found to be the cause of death in 12%, and of these approximately 27% showed papillary necrosis.

The clinical diagnosis of this disorder is rarely made but should be considered in the following types of diabetic patients [5]: (1) patients with bacteremia in whom urinary symptoms or signs suddenly develop, (2) patients who rapidly lapse into coma and show nitrogen retention without an antecedent history of pyelonephritis, (3) patients with a low-grade pyelonephritis whose condition suddenly becomes worse, (4) patients with renal colic and hematuria, and (5) patients with severe diabetic acidosis who, despite correction of the acidosis, show a gradually increasing stupor and rising nonprotein nitrogen in the absence of shock and tubular damage.

Retrograde pyelography [5] may aid in establishing the diagnosis. Deformities of the calyces are often demonstrated roentgenographically, and ring shadows of the necrotic papillae may be seen.

In the differential diagnosis, the following disorders should be considered: (1) pyelonephritis without necrosis, (2) a stone with renal colic, (3) renal tuberculosis, and (4) renal neoplasm. The latter two diseases must be considered, primarily, because of the roentgenologic changes they produce on pyelography.

The pathogenesis of renal papillary necrosis is as yet not clearly understood. The disorder has been observed in a variety of circumstances. It is generally believed that the circulation in the thin-walled and vulnerable blood vessels of the

5. Edmundson, H. A.; Martin, H. E., and Evans, N. G.: Necrosis of Renal Papillae and Acute Pyelonephritis in Diabetes Mellitus, Arch. Int. Med. **79**:148 (Feb.) 1947.

renal papillae must be interfered with to produce necrosis. Such encroachment can be produced by generalized renal vascular disease, by inflammation, by a combination of the two factors, and apparently also by increased pressure within the renal pelvis.

SUMMARY

Fragments of necrotic renal papillae were repeatedly observed in the urine of a patient with diabetes and pyelonephritis. The episodes of renal papillary necrosis occurred during a period of at least five months. The patient died in insulin shock, and autopsy revealed marked bilateral acute and chronic pyelonephritis, with advanced or complete healing of the areas of papillary necrosis. The observations on this patient indicate that papillary necrosis in itself can heal with return of renal function, and that the clinical diagnosis of renal papillary necrosis may sometimes be made by examination of the urine for fragments of necrotic tissue.

ACUTE BLASTOMYCOTIC PNEUMONIA

Report of a Fatal Case of Twenty Days' Duration

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AND
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THE SPECIAL features of the case of acute blastomycosis here reported, in contradistinction to the usual cases of fatal blastomycosis, are two, namely, the acuteness and shortness of the clinical course, 20 days, and the complete confinement of the disease to the lungs. In many fatal cases the disease is of months' duration and massive pleural blastomycosis is present about that lobe where the infection is presumed to have begun. Moreover, it is common to encounter blastomycosis of bone and subcutaneous tissues, even brain, indicating hematogenous spread.[1]

The acuteness of the disease makes necessary the clinical differential consideration of many acute pulmonary infections. Such consideration is unnecessary in most cases of generalized blastomycosis, since the nature of the disease may be suggested by the extrapulmonic lesions.

REPORT OF A CASE

Clinical History.—A 41-year-old white seamstress was admitted to the hospital on June 9, 1951, with the chief complaint of cough, fever, and pain in the chest of 11 days' duration.

The illness began on May 29, 1951, with a severe cough, fever, and pain in the right axilla. She was hospitalized in her own city, under the care of her family physician, and was given antibiotics and sulfonamides without a favorable response. She was then transferred to Birmingham for further treatment.

The patient was an obese white woman, with dyspnea and a productive cough. She appeared to be acutely ill. The skin was hot and moist. The throat was injected, and the tongue was coated and dry. Dullness over the left lung base and flatness over the right lung base were noted. Moist rales were heard in both lower lungs, and a pleural friction rub was present in the lower right chest without associated pain. Cutaneous examination revealed subsiding urticarial wheals scattered over the trunk.

The temperature was 104.2 F., the pulse rate 90 beats per minute, the respiration rate 20 per minute, and the blood pressure 130/80. The weight was 107 kg. (235 lb.).

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1. (*a*) Baker, R. D.: Fungus Infections, in Pathology, edited by W. A. D. Anderson, St. Louis, C. V. Mosby Company, 1948, Chap. 16, pp. 570-391. (*b*) Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1944. (*c*) Noojin, R. O., and Praytor, H. B.: Systemic Blastomycosis Complicated with Pregnancy, J. A. M. A. **147**:749-751, 1951.

Laboratory Data.—The white blood cell count was 17,350, with 78% polymorphonuclear cells, 20% lymphocytes, 1% monocytes, and 1% eosinophiles. Urinalysis revealed a specific gravity of 1.022, a negative reaction for sugar, and 10 mg. of albumin per 100 cc. The Kahn reaction was negative. A smear of the sputum revealed many Gram-positive cocci in clusters and many yeast forms. Two sputum specimens were negative for acid-fast bacteria when examined after concentration with a strongly alkaline solution of sodium hypochlorite ("antiformin"). Blood culture revealed Staphylococcus albus (hemolytic) which was strongly susceptible to chloramphenicol (chloromycetin®), 10 γ, and was resistant to penicillin, aureomycin, terramycin, sulfadiazine, sulfamerazine, and sulfacetamide. Stool examination revealed a few Escherichia coli trophozoites and cysts. Agglutination tests for typhoid O, typhoid H, paratyphoid A, tularemia, and paratyphoid B organisms, Brucella abortus, and typhus organisms gave negative results.

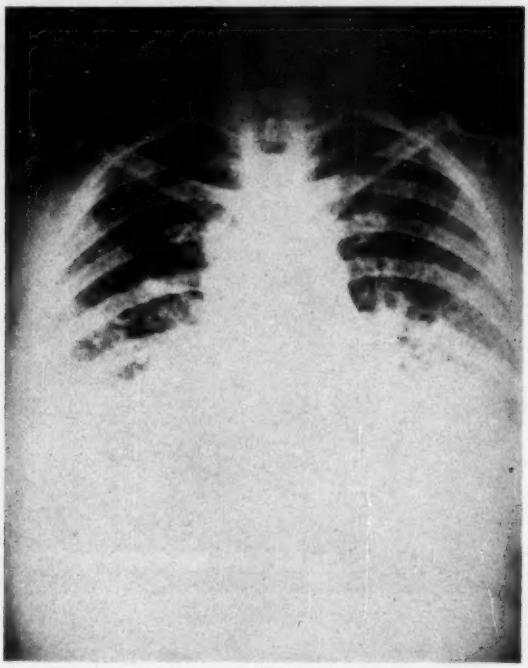

Fig. 1.—Acute blastomycotic pneumonia.

Roentgenograms.—On June 11, 1951, stereoscopic films of the chest revealed the base of the right and left lungs to be cloudy, obscuring the right and left border of the heart and the outline of the right diaphragm. The findings were interpreted as suggestive of pneumonitis of the right and left base. Four days later the shadows were more accentuated in the midpart of the right and left lungs, suggesting more infiltration (Fig. 1).

Hospital Course and Treatment.—Chloramphenicol, 500 mg., was given every four hours for four days, when its use was discontinued because of diarrhea and lack of clinical response. Penicillin, 50,000 units, was given every four hours, and the dose was later increased to 500,000 units every four hours. On June 14 aureomycin administration, 500 mg. at first and 250 mg. every four hours thereafter, was initiated. The dose of aureomycin was changed on June 15 to 500 mg. given intravenously every 12 hours. Because of the results of sensitivity tests on the blood culture, treatment with these antibiotics was discontinued, and the patient was

again given chloramphenicol, 1 gm. every three hours. Meth-dia-mer-sulfonamides (terfonyl®), 2 gm. every six hours, were also administered.

There was no favorable response to therapy at any time. The temperature ranged from 99.8 to 104 F., usually being 101 to 103 F. The pulse rate ranged from 90 to 140 per minute, but usually was in the range of 110 to 120 per minute. Respirations varied between 20 and 40 per minute. Diarrhea consisting of frequent watery stools developed on the second day after admission. The patient's respirations continued to be labored. On June 17 her cough became productive of large amounts of blood-tinged sputum, and the onset of moderate cyanosis was noted. A thready pulse was then present. She continued to be alert. In the early morning of June 18 the patient began gasping for breath, became deeply cyanotic, and had a very rapid pulse. Her temperature rose to 105 F., the pulse rate to 122, and respirations to 50, and she died at 6:15 a. m.

Fig. 2.—Blastomycosis of lungs, bilateral.

Autopsy Observations.—At autopsy there was observed an extremely obese white woman. The pubic hair was of masculine distribution, and the face showed a moderate black beard. Pleural adhesions were present over the upper and middle lobes of the lungs. There was no fluid to be found in the pleural cavities.

The lungs were many times heavier than normal. Externally they were white and nodular in the regions chiefly involved. Sectioning presented yellowish-white, nodular consolidations in both lungs, with greatest involvement of the right lower lobe and with a tendency to involve hilar rather than apical regions (Fig. 2). The cut surfaces were moist and exuded pus, but no abscess cavities were seen. The gross appearance suggested (1) tuberculosis, (2) suppurative pneumonia due to one of the pyogenic organisms, possibly Staphylococcus or Streptococcus, (3) plague, (4) tularemia, or (5) fungous infection.

Pus swabbed from the cut surface of the lung was placed on a slide, topped with a cover glass, and examined microscopically, with cutting down of the light. Numerous thick-walled organisms of Blastomyces dermatitidis were seen, some of them budding, and the diagnosis of blastomycosis was made. Blastomyces dermatitidis was later grown in culture.

The remainder of the necropsy showed that there was no spread of the infection beyond the thoracic cavity, no hematogenous spread, no involvement of ribs, and no massive involvement of the pleura. Gallstones were present. The liver was fatty and twice normal weight but showed nothing to suggest blastomycosis. The cranial cavity was not opened. In microscopic sections of lungs the Blastomycetes were seen as thick-walled organisms, some of which were budding (Fig. 3). Polymorphonuclears predominated in the exudate, though macrophages were also present. No fibrosis was seen.

Microscopic study of all the organs, and correlation with the gross findings, led to the following anatomical diagnoses: fulminating blastomycosis of lungs, bilateral; pleural adhesions; hepatomegaly (fatty liver); cholelithiasis; chronic cholecystitis; obesity, and hirsutism.

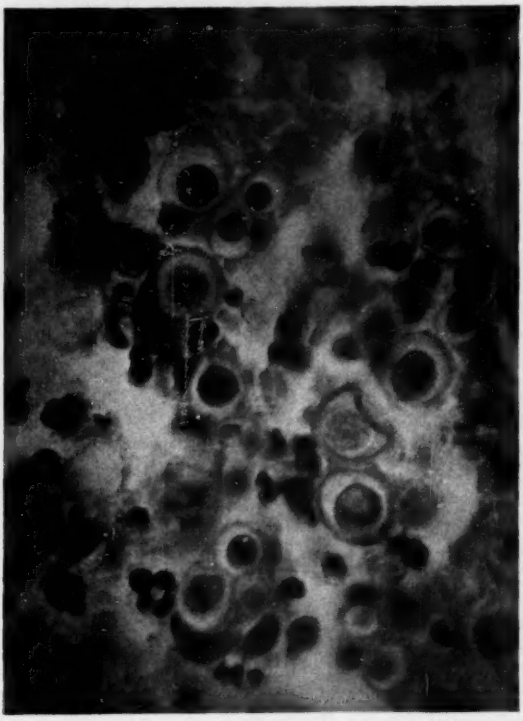

Fig. 3.—Blastomycosis of lungs. Note the "double-contoured" capsules and, in two places, forms which have recently budded.

COMMENT

There is nothing in the present case to indicate the source of the infection. A seamstress apparently should have no greater likelihood of acquiring blastomycosis than anyone else has. Blastomycosis is probably contracted through some form of contact with the fungus as it grows in nature, but little is known of its natural habitat. The disease has little or no tendency to spread from person to person, and there appears to be no danger to hospital personnel in caring for patients with the disease. Cases are on record, however, in which cutaneous lesions have developed in pathologists who performed autopsies on patients with the disease.

In our case the infection was primary in the lungs, and it is unlikely that it represented a pneumonia secondary to cutaneous or other foci.

In a review of the literature on blastomycosis by Martin and Smith, one finds that the duration of the disease in cases of fatal systemic blastomycosis was less than six months in 20 (22%) among 91 cases. The other patients lived six months to three years or more. No statement was made concerning the case having the shortest duration.[2]

The most acute case of which we have personal knowledge was one of three and one-half months' duration. The lungs from this 32-year-old Negro woman are mounted in the museum of The Medical College of Alabama, and lesions are similar to those in the case reported here, except that abscess cavities are present. Bonoff reported, in 1950, 23 cases of acute primary pulmonary blastomycosis, in 6 of which there were positive roentgenographic findings.[3] All these cases except one involved army personnel in Okinawa in November and December, 1946. At least one of the patients died and showed the features of blastomycosis at autopsy. Bonoff stated that the acute form of pulmonary blastomycosis appears to be characterized by (*a*) a prodrome of 3 to 14 days and (*b*) localized chest pain. Organisms were found in the sputum and urine, and sometimes in both.

Evidence has accumulated that the use of some antibiotics tends toward the development of moniliasis, and it is possible that in the presently reported case they did more harm than good.[4]

The definitive diagnosis of blastomycosis is made by identification of the causative fungus, Blastomyces dermatitidis. In the case presented, these organisms were seen in pus scraped from the cut surface of the lung at autopsy, and they were grown in culture. Cultures are made either on blood agar at incubator temperature or on dextrose agar at room temperature. In our case, yeast forms were seen in sputum and presumably were blastomycetes which could have been identified and cultured. Unfortunately, they were interpreted as contaminating yeast forms.

The mortality from systemic blastomycosis is high. Of 59 proved cases of the generalized disease, death occurred in 49 within five years. One of us (R. D. B.) knows of a case in which recovery occurred spontaneously. A child in North Carolina had the disease in a miliary form in the lungs with involvement of a rib and recovered completely with no treatment being given.

The gross appearances of the lungs in pulmonary blastomycosis vary. In cases of the most acute disease, represented by this report, suppurative pneumonia is observed. Those of several months' duration are more prone to present cavities.

Diffuse or focal consolidation and simulation of the picture of miliary tuberculosis may be present, or larger nodules may be noted. Thickening of the pleura may be a characteristic feature.

IMMUNOLOGY

It has been noted by Smith and others that the prognosis in blastomycosis depends upon the extent of the infection and upon the immunological response of

2. Martin, D. S., and Smith, D. T.: Blastomycosis (American Blastomycosis, Gilchrist's Disease): I. A Review of Literature; II. A Report of 13 New Cases, Am. Rev. Tuberc. **39**:275-488, 1939.

3. Bonoff, C. P.: Acute Primary Pulmonary Blastomycosis, Radiology **54**:157-164, 1950.

4. Moniliasis as a Common Complication of Biotic Therapy, Editorial, South. M. J. **44**:251-252, 1951.

the patient.[1b,c] The prognosis is best in the patient who has a positive skin test and a negative complement-fixation reaction, and poorest in the patient with a negative skin test and a strongly positive complement-fixation reaction.

Most patients with blastomycosis are hypersensitive to the fungus or fungous products, as shown by cutaneous tests with vaccines or Blastomyces extract. The cutaneous test is carried out in a manner similar to that of a tuberculin test, and the reaction should be read after 24 and 48 hours. A positive reaction has not been observed in patients without blastomycosis; however, negative reactions may occur in patients having a widespread infection. A positive intracutaneous test has been noted to become negative not infrequently during the last stages of the infection.

In most cases of extensive systemic blastomycosis the patient's sera will fix complement with suspensions or extract of Blastomyces dermatitidis. The reaction is specific when positive.

THERAPY

The same organism, Blastomyces dermatitidis, causes both cutaneous and systemic blastomycosis. The cure of cutaneous blastomycosis may be frequently accomplished, particularly if therapy is begun before the lesions have become widespread. On the contrary, the systemic disease is highly fatal.

The treatment of blastomycosis depends upon the extent of the disease and the immunological reaction of the patient. Iodide therapy is usually effective, but should not be given when the patient is hypersensitive to the organism as determined by the intracutaneous test. In such a patient the hypersensitivity should be decreased artificially by administering gradually increasing doses of vaccine. The vaccine may be autogenous or derived from any other strain. Ordinarily a 1 : 1,000 suspension in isotonic sodium chloride solution may be injected subcutaneously every other day in doses of 0.2, 0.4, 0.8, and 1 cc., to be continued for a week. After this, 0.5 cc. of vaccine may be given every two weeks. When iodide therapy is begun after desensitization, the patient is given 3 drops of potassium iodide solution three times daily, and the dosage is increased at the rate of 1 additional drop per dose daily. The dosage may have to be reduced if evidence of intoxication from the iodide therapy develops.

The additional use of x-ray therapy and suitable surgical procedures may be indicated in treatment of cutaneous lesions. In systemic blastomycosis, surgical drainage of deep lesions is desirable.

Unfortunately, none of the presently available antibiotic agents appears to be effective in the treatment of blastomycosis. Benedek, on the other hand, has reported a cure by penicillin therapy alone in a case of progressive and extensive ulcerogummatous blastomycosis.[5] The condition was of three years' duration, and the diagnosis had been confirmed by biopsy. The patient received 600,000 units of penicillin G in oil daily for 16 consecutive days, or a total dose of 9,600,000 units of penicillin. After the last injection, all lesions were healed and had remained so when observed eight months after treatment. The sulfonamides are not sufficiently effective in vitro to suggest that they would be helpful.

5. Benedek, T.: Blastomycosis (Gilchrist) (North American Type): First Case on Record Successfully Treated with Penicillin, with Survey of Literature Concerning Treatment of Deep-Seated Mycosis by Penicillin and/or Sulfonamides, Urol. & Cutan. Rev. **53**:216-220, 1949.

More recently, two of the aromatic diamidines, stilbamidine and "propamidine" (4-4'diamidinodiphenoxypropane), have been reported as affecting favorably the course of blastomycosis. Schoenbach, Miller, Ginsberg, and Long reported a favorable response in the treatment with stilbamidine of a patient with generalized blastomycosis.[6]

Colbert and associates reported the favorable response of a patient with cutaneous blastomycosis to the use of "propamidine."[7]

At present in Jefferson-Hillman Hospital, Birmingham, Ala, there is under therapy a patient with systemic blastomycosis who is receiving stilbamidine, 150 mg. intravenously daily. After several weeks his course has been favorable, although he is not yet considered cured.

Corticotropin (ACTH) has been used in the treatment of blastomycosis and tends to break down the granulomatous tissue; however, since no chemotherapeutic agent has heretofore been available to destroy the blastomycete, the use of corticotropin alone has not been recommended.

The agents now available for treatment of systemic blastomycosis appear to have improved the prognosis usually entertained 10 or 15 years ago.

SUMMARY

A case of blastomycosis is reported in which the entire clinical course lasted only 20 days. The unusually short course made the differential diagnosis from other forms of acute pneumonia very difficult. The disease was seen at autopsy to be confined entirely to the lungs. The pathologic, immunological, and therapeutic features of the disease are discussed.

ADDENDUM

Since the preparation of this manuscript one of us (R. O. N.) has successfully treated with stilbamidine one patient with extensive cutaneous blastomycosis and two patients with systemic blastomycosis. One of the patients, however, has now had for five months a severe neuropathy of the fifth cranial nerve attributable to stilbamidine.

6. Schoenbach, E. B.; Miller, J. M.; Ginsberg, M., and Long, P. H.: Systemic Blastomycosis Treated with Stilbamidine: Preliminary Report, J. A. M. A. **146**:1317-1318, 1951.

7. Colbert, J. W., Jr.; Strauss, M. J., and Green, R. H.: Treatment of Cutaneous Blastomycosis with Propamidine; Preliminary Report, J. Invest. Dermat. **14**:71-73, 1950.

News and Comment

ANNOUNCEMENTS

International Academy of Proctology 1952 Award Contest.—The International Academy of Proctology takes pleasure in announcing its annual cash prize and certificate of merit award contest for 1952-1953. The author of the best unpublished contribution on proctology or allied subjects will be awarded $100.00 and a Certificate of Merit. Certificates will be awarded also to physicians whose entries are deemed of unusual merit.

This competition is open to all physicians in all countries, whether or not affiliated with the International Academy of Proctology. The winning contributions will be selected by a board of impartial judges, and all decisions are final.

The formal award of the first prize, and a presentation of other Certificates, will be made at the Annual Convention Dinner Dance of the International Academy of Proctology in May, 1953.

The International Academy of Proctology reserves the exclusive right to publish all contributions in its official publication, *The American Journal of Proctology and Gastroenterology.*

All entries are limited to 5,000 words, must be typewritten in English, and must be submitted in five copies. All entries must be received no later than the first day of April, 1953. Entries should be addressed to the International Academy of Proctology, 43-55 Kissena Blvd., Flushing 55, N. Y.

Prize for Paper on Diabetes.—The American Diabetes Association offers a $250.00 prize to medical students and interns for a paper on any subject relating to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment, or a review of the literature.

This incentive is particularly apropos in the field of diabetes, since Dr. Paul Langerhans made his studies of the pancreas, describing the islets that bear his name, while he was an undergraduate student in Berlin in 1869, and Dr. Charles H. Best, while a graduate student, was co-discoverer of insulin in 1922.

Manuscripts must be submitted on or before April 1, 1953, to the Editorial Offices of *DIABETES: The Journal of the American Diabetes Association,* 11 West 42nd St., New York 36. The papers will be reviewed by the editorial board, which will take into consideration the value of the material and method of presentation in selecting the best paper.

The award of $250.00 has been made possible through the generosity of the St. Louis Diabetes Association, an affiliate of the American Diabetes Association.

Medical Officers Examination.—The United States Civil Service Commission has announced a medical officer examination for filling the positions of rotating intern, psychiatric resident, and general practice resident in St. Elizabeth's Hospital, Washington, D. C.

The rotating intern positions pay $2,800 a year; psychiatric resident, $3,400 to $4,200, and general practice resident, $3,400 to $3,800 a year. Education and training are required. No written test will be given. The maximum age limit is 35 years (waived for veterans).

Full information and application forms are available at most first- and second-class post offices and at the U. S. Civil Service Commission, Washington 25, D. C. Applications will be accepted until further notice by the Executive Secretary, Board of U. S. Civil Service Examiners, St. Elizabeth's Hospital, Washington 25, D. C.

Books

Angiocardiography as a Diagnostic Aid in Congenital Heart Disease. By J. W. C. DeGroot, M.D. No price given Pp. 108, with 20 illustrations. Systemen Keesing, Amsterdam, Netherlands, 1951.

This monograph on angiocardiography is composed of two parts.

Part I consists of a review with concentration on the more important facts from the numerous articles published on this subject over the past 20 years. This has been accomplished quite well in the short space of 40 pages and is supported by a fairly complete bibliography. The review proceeds in an orderly fashion, covering methods, apparatus, hazards, and the value of angiocardiography.

In Part II the author presents 12 case reports on congenital heart disorders, with description of his methods, results, and conclusions. Adequate angiocardiograms are presented illustrating these cases.

The monograph would appear to be very useful to students and to physicians desiring a summarized knowledge of angiocardiography.

Nutrition and Climatic Stress, with Particular Reference to Man. By H. M. Mitchell and Marjorie Edman. Price, $6.75. Pp. 234, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

This monograph is a review of the literature pertaining to the interrelationship of nutrition and climatic stress. The material, originally prepared for the Quartermaster Food and Container Institute of the Armed Forces, has been revised to consider references up to about Oct. 1, 1949.

The chief climatic stress factors discussed are cold, heat, and altitude. For each there is a discussion of the general physiological effects of the stress factor, its effect on nutrient requirements, and the effect of the diet on tolerance to the stress. Even though the review is concerned chiefly with man, a large amount of animal experimentation is discussed. The authors emphasize that often there is a considerable discrepancy between the results of animal and those of human experimentation. In certain situations, "animal experimentation has furnished an unsafe guide to human responses to climatic and dietary changes and interactions." The authors conclude that there is a great need for further studies with human subjects, especially carefully controlled experiments, in many aspects of this problem. For example, the quantitative effect of climatic factors on the nutritive requirements of man is considered to be largely an unexplored field of study.

This monograph will be of considerable value not only as a critical review of present-day knowledge concerning nutrition and climate but also as a reference source with its 60-page bibliography.

A Manual of Parasitology for Medical Students and Beginners. By Mark M. Shapiro, M.D. Price, $5.50. Pp. 140, with illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1951.

This manual is well plannned for use by those for whom it was written, medical students and beginners in the study of parasitology. It is not a lengthy and exhaustive study of the subject, nor is it a good reference book. It is, rather, a brief and limited study of a few aspects of the science. The author considers only those organisms which are of medical significance, either as causative agents of disease or as nonpathogens requiring differentiation from the former. He concentrates on the morphology and life cycle, with emphasis on their differential aspects. There is essentially no discussion on the clinical aspects of parasitic infections.

The book is clearly written, with drawings of the parasites in their various stages of maturity. A section on diagnostic methods is included, with a discussion of smear and staining technique and of the serological tests that may be used.

To cover the science of parasitology adequately in a book of this size is, of course, an impossibility. But the medical student or beginner has little desire for a complete coverage

of the subject. His greatest need is a well-sifted, concise, and condensed study of the science; a book unencumbered with minor technicalities, and a book, therefore, admittedly inadequate for advanced study. The need is adequately met by this manual.

Kwashiorkor in Africa. By J. F. Brock and M. Autret. World Health Organization Monograph Series No. 8. Price, $1. Pp. 78. World Health Organization, Palais des Nations, Geneva; Columbia University Press, International Documents Service, 2960 Broadway, New York, 1952.

This monograph, sponsored by the World Health Organization with the cooperation of the United Nations Food and Agriculture Organization, is a significant contribution to knowledge of kwashiorkor, an important nutritional disorder of unknown causation prevalent in tropical and subtropical countries. Findings were gleaned from a survey in 10 areas of Central Africa, from the world literature, and from the experiences of one of the authors in South Africa. Essential features of the kwashiorkor syndrome among indigenous Africans are summarized as follows: (*a*) retarded growth in the late breast-feeding, weaning, and postweaning ages, (*b*) alterations in skin and hair pigmentation, (*c*) edema, (*d*) fatty infiltration, cellular necrosis or fibrosis of the liver, and (*e*) a heavy mortality in the absence of proper dietary treatment. Dermatosis was commonly present; gastrointestinal disorders, mental apathy, anemia, and atrophy of the acini of the pancreas often occurred. The characteristic clinical findings are well depicted in photographs.

From a study of feeding practices, food consumption, and therapeutic tests, the authors conclude that kwashiorkor appears to be due to deficiency of some factor or factors supplied by foods containing animal protein or vegetable protein of high biological value. The relation between protein requirements and protein available in the diet of children with kwashiorkor is discussed in detail. An interesting finding was the very low methionine content of the daily food supply in areas where kwashiorkor is common. Skim milk powder is reported to be effective therapy, and a number of milk substitutes which can be produced locally are being investigated. Recommendations for prevention and treatment and for further research on this problem are presented. It is suggested that kwashiorkor, and cirrhosis, and primary carcinoma of the liver may be etiologically related in view of their world distribution.

Recent Advances in Clinical Pathology. Second edition. Edited by S. C. Dyke. Price, $6. Pp. 575, with 36 illustrations and 37 plates. The Blakiston Company (Division of Doubleday & Company, Inc.), 1012 S. Walnut St., Philadelphia 5, 1951.

This book emphasizes recent developments in laboratory medicine in a direct, concise style supplemented with informative illustrations. The contents are divided into five sections, namely, bacteriology, biochemistry, hematology, histology, and a special section on laboratory design and apparatus. In each part there is reference to new as well as to established procedures, including those for both research and routine use. Of most importance are the technical directions that are included in detail. The reference list for each section is thorough but selective.

The section on bacteriology emphasizes those procedures useful in the diagnosis of the enteric fevers. Methods for rapid identification of tubercle bacilli include low-power microscopy with the green-filter technique and the use of fluorescent staining. A simplified and useful classification of the fungi is included, as well as suggestions for their identification. The principles of the laboratory diagnosis of viral infections are discussed with commendable emphasis on the procedures of practical usefulness.

The section on biochemistry deals with liver-function tests, the disturbances and correction of electrolyte imbalance, useful recommendations for microchemical blood analysis, and a section on the hemolytic and deficiency anemias. The discussion of hemoglobinometry includes some methods of great inaccuracy, but these are not emphasized or recommended. The chapter on radiation exposure indicates the maximum safe dose of each isotope, as well as the methods of protection at autopsy and the techniques of proper disposal.

A considerable portion of the book is entitled histology. The serial illustrations of the cyclic endometrial changes may be useful. The section on bladder tumors commendably suggests that papillomas be so designated when the malignant changes are not present. There is a practical section on histochemical methods for the identification of tissue pigments. The

wet-film technique is described favorably in comparison with the frozen-section method, particularly for identification of tumors of the central nervous system at the time of operation.

The book is characterized by its clear discussion of the recent developments in laboratory medicine that are of practical use, as well as by its presentation of the full details of the techniques employed. It is believed that this edition will find wide use by those practicing clinical pathology.

Surgical Forum: Proceedings of the Forum Sessions, Thirty-Seventh Clinical Congress of the American College of Surgeons, San Francisco, California, November 1951. Edited by the Surgical Forum Committee, with various contributors. Price, $10. Pp. 667, with 290 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

In the fall of 1951, the American College of Surgeons held its annual Surgical Forum. This appears to have consisted of a series of short presentations, usually by young men, on a wide range of subject matter pertaining to surgery and to surgical research. This volume presents the proceedings.

The book is interesting in several ways: It is well printed, well edited, and well illustrated, so that it is read easily; it includes 116 short papers, as well as abstracts of others that presumably were not read because of time; the list of authors is made up of 341 names, mostly those of surgeons on lower rungs of the academic ladder, but a few are those of physicists, chemists, physiologists, or pharmacologists, and a very rare one is that of an internist.

The subject matter is well classified so that one can easily get an idea of how surgeons are attacking even the most inaccessible parts of the body either directly or by ingeniously contrived experiments. Above all, however, one is struck with the manner in which surgical knowledge is advancing—no longer by way of improved mechanical techniques, but by the application of basic medical sciences to the problems at hand. On the whole, the volume deserves a place in any medical library.

Streptomycinresistente Tuberkelbacilstammer. By Einar Espersen. No price given. Pp. 153, with 85 illustrations and tables. Ejnar Munksgaards Forlag, Nørregade 6, København, K., 1951.

This is a study on the effect of streptomycin, paraaminosalicylic acid, and sulfathiazole on tubercle bacilli. The findings of the author are essentially similar to those of other investigators:

Streptomycin-resistant strains of the tubercle bacillus are morphologically identical with corresponding streptomycin-sensitive strains.

Different strains develop resistance in vitro at a varying rate and in different degrees. Strains that have not been exposed to streptomycin may include highly streptomycin-resistant variants.

The growth of streptomycin-resistant strains on streptomycin-containing medium proceeds morphologically just as on normal medium. Such strains do not consist exclusively of organisms with the same degree of resistance but include also more sensitive cells.

Streptomycin resistance is specific, and streptomycin-resistant strains form no streptomycin-inactivating substance.

Streptomycin-resistant strains are affected morphologically by paraaminosalicylic acid as normal strains are, and their sensitivity to the drug is identical with that of corresponding sensitive strains.

Acquired resistance to paraaminosalicylic acid appears to occur frequently, and strains resistant to the drug are still streptomycin sensitive.

In vitro, the combinations of streptomycin and penicillin, of streptomycin and sulfathiazole, and of streptomycin and paraaminosalicylic acid have a synergistic effect on tubercle bacilli.

The 1951 Year Book of Pathology and Clinical Pathology. Section on pathology edited by Howard T. Karsner, M.D., LL.D. Section on clinical pathology edited by Arthur H. Sanford, M.D. Price, $5.50. Pp. 454, with 147 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

This useful little book, which reviews the progress in pathology and clinical pathology during 1951, lives up to the fine reputation earned by previous editions. The section on pathology

covers both general and special pathology. It includes special articles on epidemic hemorrhagic fever and the pathogenesis of arteriosclerosis in human beings and birds, as well as numerous abstracts of articles covering the wide field of pathology. The section on clinical pathology gives new techniques in hematology, chemistry, bacteriology, serology, parasitology, and clinical microscopy.

The abstracts are representative of recent work in the specialty of pathology, are well written, and are complete enough to be useful. The editors usually indicate when the original article should be consulted for details and usually give the general background against which the article should be critically evaluated. This is most helpful. In the abstracts of the articles dealing with clinical pathology, the details of technique are given in sufficient detail that the tests can be used in the laboratory.

Such books as these are extremely helpful in keeping one up to date in the fields of pathology and clinical pathology. All those concerned with the preparation of this book deserve praise and a vote of confidence for the splendid job which they have done.

Textbook of Medicine. Tenth edition. Edited by Sir John Conybeare and W. N. Mann. Price, $8. Pp. 929, with 31 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

Those who are familiar with the first edition of "Conybeare" (1929) will hardly know it in its 1952 form. It is a considerably enlarged volume; 17 authors now appear in the table of contents.

This is really an excellent book. Well written and concise, it gives most of the essentials. In places one could wish for a little more detail in therapeutic directions. The section on gastrointestinal disease, as is true of all textbooks, is the weakest, perhaps from the nature of the subject. The section on gastritis is certainly outmoded. The chapters on the heart seem somewhat split up, and in the section on the treatment of congestive failure one finds no direct discussion of digitalis.

It is easy, however, to carp at small points. On the whole, praise is due to the editors and authors for a good job.

Veterans Administration Technical Bulletins Series 10. Volume IV, 1950. No price given. United States Government Printing Office, Washington 25, D. C., 1951.

Since 1946 the Veterans Administration has been issuing technical bulletins, which in essence are timely and interesting articles written by men well known and respected in the medical profession. Eight bulletins written in 1950 and the first two that appeared in 1951 are presented in a compact and nicely bound book, each bulletin constituting a different chapter.

Thorough coverage of the subject characterizes each bulletin. Such subjects are included as "The Treatment of Coronary Thrombosis with Myocardial Infarction." by Irving S. Wright, M.D.; "The Diagnosis and Treatment of Adrenal Cortical Insufficiency," by Peter Forsham, M.D., and George Thorn, M.D.; "Some Aspects of Medical Planning in Atomic Warfare," by George Lyon, M.D.; Treatment of Cardiac Arrest," by Claude S. Beck, M.D., and "The Pathologic Physiology and Treatment of Edema," by Louis G. Welt, M.D., and Donald W. Seldin, M.D., and five other articles of equal interest. Each bulletin is summarized and followed by an excellent bibliography.

The book constitutes an excellent up-to-date review of many interesting and timely subjects.

The Unipolar Electrocardiogram: A Clinical Interpretation. By Joseph M. Barker, M.D., F.A.C.P. Price, $10. Pp. 655, with 458 illustrations. Appleton-Century-Crofts Company, Inc., 35 W. 32d St., New York 16, 1952.

This book answers a real need for an up-to-date presentation which, starting from "first principles," covers the theoretical and practical aspects of electrocardiography in a systematic, but not encyclopedic, manner. It summarizes unofficially, as it were, many of the concepts and writings of the school which under the leadership of Frank Wilson has contributed so profoundly to our knowledge of electrocardiography.

The first six chapters (some 130 pages) deal with the fundamental aspects of the subject, including electrophysiology, a discourse on the various leads, the Einthoven triangle, and

electrical axis. This section is followed by a systematic presentation of bundle branch block, myocardial infarction, myocardial ischemia, ventricular hypertrophy, the auricular complex, the arrhythmias, anomalous auriculoventricular conduction, and miscellaneous clinical manifestations. The concluding chapter is on reading, reporting, and coding of the electrocardiogram. A bibliography is appended, but it has been selected with obvious prejudice for those publications which coincide with the author's own views. There is a good index.

The reviewer questions the wisdom of a long chapter on anomalous auriculoventricular conduction, while the effects of electrolyte imbalance are considered rather briefly. A very sketchy presentation of the electrocardiogram in congenital heart disease is presumably a reflection of the author's lack of interest and experience in this field. The half-page discussion of the vectorcardiogram, obviously grossly inadequate, should have been omitted.

The book is remarkably free of misspellings and other errors. The many diagrams are excellent, the electrocardiograms well selected and reproduced, and the publishing details of a high quality.

This book can be recommended to all those who are interested in electrocardiography. It will appeal especially to those who have in the past found an unbridged gap between the "primer" or "introductory" type of book and the detailed, highly technical papers in the specialty journals. In addition, it will provide illumination and stimulation to the many physicians who over the years have accumulated a vast fund of knowledge of practical electrocardiography, but who have—in ignorance or in mistaken fear of "theory"—avoided and neglected the more scientific approach to this subject.

Spatial Vectorcardiography. By Arthur Grishman, M.D., and Leonard Scherlis, M.D. Price, $6. Pp. 217, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

This monograph is one of a series which, according to the publisher, is intended to present the practical results of research in special fields of medicine. Spatial vectorcardiography undoubtedly qualifies as such a field, but, if "practical" implies clinicaly useful results, the intention of the publisher is not realized. Wide use of the vectorcardiogram should await proof that it exceeds the range of usefulness of the electrocardiogram, and as yet such proof is inadequate.

For example, the difficult problem of recognizing posterior infarction, in which it is hoped the vectorcardiogram will be of assistance, is dismissed by these authors with the statement that such lesions may be recognized by "increased anterior displacement of the QRS sE-Loop." Without pathological confirmation, which is not furnished, such a statement is both meaningless and misleading.

The book consists of 12 chapters, the first 4 of which contain theoretical and technical discussions of vectorcardiography, while the remainder present the authors' findings in a variety of cardiac states.

In the theoretical and technical discussion the controversial subject of lead placement is treated in an opinionated manner, and judgment of the authors' opinions should be made only by those thoroughly familiar with the special problems of this method.

In the sections presenting the authors' findings, the lack of autopsy data and the failure to indicate the number of subjects studied are major deficiencies.

This book is of interest to those engaged in vectorcardiographic research as a statement of the authors' opinions, but it has little import for the clinician.

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1. Humphreys, P., et al: Angiology 3:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med., 52:2012-2014 (Aug. 15) 1952. 3. Perlman, A.: Angiology 3:16 (Feb.) 1952. 4. Samuels, S.S., et al.: Angiology 3:30 (Feb.) 1952.

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Ward, E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S.,
Proc. Staff Meet. Mayo Clin. **26**: 361, Sept. 26, 1951.

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